THE CHEMISTRY OF SYNTHETIC DRUGS

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OF

SYNTHETIC DRUGS

BY

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PREFACE TO SECOND REVISED EDITION

As was stated in the Preface to the First Edition, thi book contains an account of the main facts concernin the chemical nature of synthetic drugs and the guidin principles which are used in their production. New drug are constantly being introduced, and though many of ther are well known and widely used, their chemical nature i often unknown even to chemists possessing a good knowledge of general organic chemistry. For this reason ther appeared to be some need for an attempt to increase the interest of chemists in a branch of their subject which is very interesting in itself, and which also affords scope for commercial application.

Before the war, the manufacture of synthetic drugs was practically confined to Germany, but since 1914 considerable progress has been made with their production in this country. The manufacture of synthetic organic chemicals on a large scale presents many difficult problems, and it is gratifying to find that most of these have been successfully overcome by British chemists in so short a time, and working under such difficult conditions. Nevertheless, it will probably be necessary to give some form of protection to this important growing industry for some years after the conclusion of peace if it is to hold its own in competition with the vast and highly organized German organic chemical industry.

This book contains more than a mere description of the chemical nature and mode of preparation of many synthetic drugs. For a scientific understanding of the subject, it is necessary to pay considerable attention to reactions taking place between the drug and the living organism whenever these can be traced, and to the relation between the chemical character of a substance and its pharmacological action, even though this relation is neither so complete nor so simple as might be desired, and is confined to only a few of the numerous chemical compounds that are used as drugs.

It has been thought desirable to mention briefly the therapeutic effect of most of the chief drugs, so that readers may gain some idea of their relative importance, but no attempt has been made to deal in any detail with pharmacology or therapeutics, subjects which lie quite outside the scope and aim of this book. It has been neither possible nor necessary to mention all the synthetic drugs which have been prepared in recent years, as many of them possess neither scientific nor therapeutic value.

Besides the practical importance and inherent interest of the subject, it may also be of great value as a means of opening up new channels of research and of discovering new types of compounds. Just as the discovery of the coal-tar colours gave a great stimulus to the study of aromatic compounds, so the efforts to produce new drugs have led to a greatly increased knowledge of certain types of compounds, as for example those containing carbon united to arsenic and antimony.

Further, it is hoped that this volume may prove of interest to those medical men who desire to obtain more unbiassed information concerning the application of chemistry to therapeutics and pharmacology than can be obtained from the countless trade circulars with which they are, or used to be, inundated.

The arrangement of the subject-matter invariably presents difficulties in a book of this kind. No plan can be entirely logical and satisfactory, but it is hoped that the arrangement here used will be found a convenient one. Cross references have been inserted wherever possible.

I wish to express my thanks for the encouraging reception given to the first edition of this book, and especially to those readers who have been kind enough to point out omissions or errors. In addition to minor alterations, certain sections have been largely rewritten on account of recent developments of the subject, and some entirely new sections have been added.

My most grateful thanks are due to Mr. H. W. Vernon for his help in correcting the proofs of this edition.

P. M.

May, 1918.

INDEX.

ACETALDEHYDE, 28, 51.
Acetanilide, 67, 68.
Acetomorphine, 110.
Acetone, 59.
— behaviour of, in organism, 38.
Acetone-chloroform (see Chloretone).
Acetophenone (see Hypnone).
Acetopyrine, 66, 157.
Acetoxime, 26.
Acetozone, 190.
p-Acetylamino-phenol, 70, 73, 164.
Acetylamino-phenol acetamide, 77.
Acetylamino-phenyl benzoate, 77.
Acetyl-atoxyl, 204-205.
Acetyl-ethylamino-phenyl acetate, 77.
Acetyl-*p*-hydroxyphenylethylamine, 148.
Acetyl-salicylic acid, 157, 158.
— — — esters of, 163.
Acid groups, effect of, 29.
Acitrin, 224.
Acriflavine, 173.
Adalin, 129.
Adrenaline, 34, **129-136**, 141, 150.
— methylene and methyl ethers of, 133-135.
iso-Adrenaline, 134.
Adrenalone, 131, 147, 149-150.
Agurin, 217.
Airol, 173, **178**, 183.
Albargin, 194.
Alcohol (see Ethyl Alcohol).
Alcohols, primary, secondary, and tertiary, action of, 23, 55, 56.
behaviour of, in organism, 38.
Aldehyde groups, effect of, 28.
Alizarine-Bordeaux, 226.
Alkyl groups, effect of, 17, 19.
N-Alkyl quinoline derivatives, 64.
Allyl-thiourea, 208, **239**.
Allyl-tri-methyl-ammonium hydroxide, 32.
Aloe, 225.
Aloïn, 227.
Alum, 195.
Aluminium compounds, 195.
Alumnol, 195.
Alypine, 99, **100**.
Amidopyrine (see Pyramidon), 66.
Amino-acetic acid (see Glycine).
Amino-aceto-catechol, 149.
Amino-acetopyrogallol, 150.
Amino-acetoveratrone, 119, 120.
Amino-acids, 38, 39, 42, 138.
m-Amino-benzoic acid, 30.
p-Amino-benzoic acid, derivatives of, 102-103.
γ-Amino-butyric acid, 79.
Amino-ethanolcatechol, 149.
Amino-ethyl-catechol, 149.
Amino-ethyl-pyrogallol, 149.
Amino-hydroxy-benzoic acid, esters of, 100, 101.
1-Amino-naphthalene-4 arsinic acid, 206.
8-Amino-naphthol (1)-3-6 disulphonic acid, 172.
8-Amino-paraxanthine, 219.
p-Amino-phenol, 36, 68, **70**, 71-77.
p-Aminophenyl-arsenious oxide, 201, 209.
p-Aminophenylarsine, 209.
bis-*p*-Aminophenylarsinic acid, 205.
p-Aminophenylarsinic acid (see also Atoxyl and Arsanilic Acid), 203.
p-Aminophenylstibinic acid, 215.
8-Amino-theophylline, 219.
Amino-tolyl-arsinic acids, 205, 206.
bis-2-Amino-tolyl-5-arsinic acid, 205.
δ-Amino-valerianic acid, 79.
Ammonium bases, effect of, 5, 15.
Amphotropin, 177.
Amygdophenine, 75.
Amylamine, 147.
iso-Amylamine, 137.
Amylene, action of, 19.
— hydrate, 56.
tertiary Amyl-urea, 56.
Anæsthesine, 102.
Anchoring groups, theory of, 6, 7, 10, 11, 171.
Aniline, 63, **67-68**.

Aniline, oxidation of, in organism, 38, 68.
Anisic acid, 20.
— aldehyde, 139.
o-Anisidine, 165.
Anthragallol, 226.
Anthranil arsinic acid, 206.
Anthrapurpurin, 222, 227.
Anthraquinone derivatives, 225-227.
Antifebrin (see Acetanilide).
Antiluetin, 216.
Antimony compounds, 214-216.
— finely divided metallic, 216.
Antipyrine, 20, **65**, **66**.
Antithermin, 67.
Aperitol, 228.
Apocodeine, 111, 112.
ψ-Apocodeine, 111.
Apomorphine, 107, **111**.
Arecaidine, 11.
Arecoline, 11.
Argentamin, 194.
Argonin, 194.
Aristol, 184.
Aristoquinine, 84.
Arrhenal, 203.
Arsacetin 200, 204, 208.
Arsamin, 204.
Arsanilic acid, 204, 205, 208 (see also Atoxyl).
Arsenious oxide, 197.
— — aromatic derivatives of, 201.
1-1-Arsenoanthranol, 213.
Arsenobenzene derivatives, 201, 202, 209.
Arsenobenzol (see Salvarsan).
Arsenophenol, 209.
Arsenophenylglycine, 209.
Arsenostibine compounds, 215.
Arsinic acids, 203, 208.
Arsonium bases, 15, 17.
Aryl-stibinic acids, 215.
Aseptol, 154.
Asparagine, 34.
Aspirin (see Acetyl-salicylic acid).
Asterol, 193.
Atophan, 223.
Atoxyl, 197, 198, 199-201, **203-204**, 208.
Atrolactinic acid, 89.
Atropine, 12, 34, 86, **88**, 89.

BAGLIONI's theory of narcosis, 49.
Barbaloïn, 226.
Barbitone (*s.* Veronal), **57**.
Bart's reaction, 208, 215.
Basic nitrogen groups, effect of, 26.
m-Benzaminosemicarbazide, 67.
Benzanilide, 68.
Benzene, behaviour of, in organism, 39.
— hydrocarbons, action of, 19.
Benzidine dyes, 171, 172.
Benzoic acid, behaviour of in organism, 42.
Benzonaphthol, 163.
Benzophenone, 59.
Benzosalin, 163.
Benzosol, 167.
Benzoyl-ecgonine, 92.
— — esters of, 92, 93.
Benzoyl-phenylethylamine, 139.
Benzoylsalicylic acid, methyl ester of, 163.
Benzyl-morphine (see Peronine).
Berberine, 116, **123-124**.
Betol, 163.
Biogen, 190.
Bismuth, 178.
— emetine iodide, 128.
Bleaching powder, 179.
Boric acid, 190.
Borneol, 233, **235**, 236.
— carbonate, 166.
— esters of, 236.
Bornyl chloride, 234.
Bornyval, 236.
Brilliant green, 172.
Bromalbin, 189.
Bromal hydrate, 46, 47, **55**.
Bromdiethylacetyl-urea, 189.
Brometone, 54.
Bromides, alkaline, 188.
Bromipin, 188.
Bromoform, **51**, 182.
Bromoglidine, 189.
α-Bromo-isovalerianic acid, 189.
— — — borneol ester, 189.
Bromo-lecithin, 238.
Bromo-phenacetin, 76.
Bromural, 189.
Brovalol, 189.
Butyl-chloral, 54.
— — hydrate, 46, 47.
tertiary Butyl-urea, 56.

CACODYL, 202.
Cacodyliacol, 167, 203.
Cacodylic acid, 202.
Cadaverine, 147.
Caffeine, 13, **217**.
— acetylamino derivatives of, 217.
iso-Caffeine, 219.
Calomel, (see Mercurous chloride).
Camphor, 174, **233-235**.
Canadine, 116.

Carbamic acid, 26.
"Carbon," 174.
Carbon-tetrachloride, 24, **51**.
Carvone, 32.
Cascara, 225.
Catechol, 20, 130, 164.
— carbonate, 166.
Cephaeline, 127, 128.
Changes in the organism and their relation to the activity of a drug, 12, 13.
Chemico-therapy, 170, 174, 197.
Chinosol, 175.
Chloracetyl-catechol, 131.
Chloral, 51.
— behaviour of in organism, 37, 39, 41.
Chloralamide, 53.
Chloramine antiseptics, 179-181.
Chloramines, 179-181.
Chloramine-T, 180.
Chloral-ammonia, 53.
Chloral-formamide, 53.
Chloral-hydrate, 46, 47, **51**, 52.
Chloral-imide, 53.
Chloral-urethane, 54.
Chlorcosane, 181.
Chloretone, 54.
Chlorine compounds, 179-181.
1-Chloro-2 amino-phenyl-5 arsinic acid, 206.
Chloroform, 24, **50**, 172.
8-Chloro-theophylline, 219.
Choline, 32.
Chrysophan, **225**, 232.
Chrysophanic acid, 225, 227.
Cinchonine, **82**, 83, 84.
Cinnamic acid, 159.
Citarin, 223.
Citric acid derivatives, 177, 223.
Cocaine, 2, 11, 35, 86, **91**, 92, **93**, 94, 136.
a-Cocaine, 2, 35, **96**.
Codeine, 104, **105-109**, 120.
— methyl bromide, 110.
Codethyline (see Ethylmorphine).
Collidine, 33.
Colloidal mercury, 192.
— silver, 194.
— — chloride, 194.
Coniine, 80.
Cordal (see Tribromsalol).
Corydaline, 118, **126**.
Cosaprin, 69.
Cotarnine, 116, 122, 123, **125**, **126**, 127.
Coto-bark, 230.
Cotoïn, 231.
o-Coumaric acid, 159.
Creolin, 152.
Creosoform, 169.
Creosol, 164, 165.
— carbonate, 166.
Creosote-carbonate, 166.
Creosote-phosphite, 167.
o-, *m*- and *p*-Cresols, **152**, 158, 159.
Cresotinic acid, 153, 167.
Cresylic acid, 153.
Croton-oil, 212.
Crum Brown and Fraser, law of, **5**, **80**, 148.
Cryogenin, 67.
Cryptopine, 128.
Cupreine, **82**, 84.
Curare, **5**, 148.
Cyanacetic acid, 28.
Cyanogen chloride, 28.
— radicle, effect of, 28.
Cyclic ureides, 57.
Cycloform, 102.
Cystamine, 176.
Cystazol, 177.
Cystogen, 176.
Cystopurin, 177.

DAKIN's solution, 179.
Dermatol, 178.
Dextroform, 176.
Diacetin, 46, 47.
Diacetonamine, 97.
Diacetyl-morphine, 109, 110.
Diacetyl-phenetidine, 74.
p-Diamino-arsenobenzene, 209.
p-Diamino-dihydroxyarsenobenzene, 209.
3-3-Diamino-4-4′-dihydroxystibinobenzene, 215.
Di-*o*-aminophenyl disulphide, 239.
sym-Diamyl-urea, 56.
Diaspirin, 157.
Dichloramine-T, 180, 181.
Diethylamine, 102, 103.
Diethylaminoethyl alcohol, esters of, 102, 103.
Diethyl-barbituric acid (see Veronal).
Diethyl-ketone, 59.
Diethyl-malonylurea (see Veronal).
Diethyl-sulphone-methane, 46.
Digitalin, 232.
Digitalis, 232.
Digitoxin, 232.
Dihydro-papaverine, 118.
2-4-Dihydroxy-ω-amino-acetophenone, 149.
Dihydroxy-diamino-arsenobenzene, 209, **210**-214.

2-4-Dihydroxyphenylarsinic acid, 213.
3-4-Dihydroxyphenylethylamine, 138, 139, 140, **141**, 142, 149, 150.
3-4-Dihydroxyphenylethylmethylamine, 141, **142**, 149, 150.
Dihydroxypiperazine, 222.
4-5-Dimethoxy-2β-methylaminoethyl-benzaldehyde, 126.
6-7-Dimethoxy-2-methyl-3-4-dihydro-isoquinolinium chloride, 126 (see Lodal).
6-7-Dimethoxyisoquinoline-1-carboxylic acid, 127.
4-Dimethyl-amino-antipyrine (see Pyramidon).
1-4-Dimethyl-2-amino-phenyl-5-arsinic acid, 206.
p-Dimethylamino-phenyl arsinic acid, 207.
Dimethyl-piperazine, 222.
Dimethyl-sulphone-diethylmethane ("reversed" sulphonal), 60.
Dimethyl-sulphone-dimethyl-methane, 46.
Dimethyl-sulphone-ethyl-methane, 60.
Dimethyl-sulphone-methyl-ethyl-methane, 60.
Dionine 110 (see also Ethyl-morphine).
Diphenyl, 19.
— tartrate, 220.
Diplosal, 157.
Dipropyl-malonyl urea, 57.
Disalol, 163.
Dispermin, 222.
Distribution coefficient, 46.
Diuretin, 217.
Dormigene, 189.
Dormiol, 53.
Dulcin, 21.
Duotal, 165-167.
Dyestuffs, 7, 170-174.

Ecgonine, 88, 91, 92.
— methyl ester, 92, 93.
α-Ecgonine, 95.
Ehrlich's theory of the action of drugs, 6, 7, 170, **171**-174.
Ektogen, 190.
Emetine, 127, 128.
— bismuth iodide, 128.
Emodin, 225.
Epicarine, 154.
Epinephrine, 129, 136 (see also Adrenaline).
Epinine (see 3-4-Dihydroxyphenylethylmethylamine).
Epiosine, 116.
Ergamine, 139.
Ergot, 129, **137**.
Ergotoxine, 138.
Ericin, 162.
Erythrol-tetra nitrate, 25.
Ether (see Ethyl ether).
p-Ethoxyphenyl urethane, 75.
Ethyl alcohol, 23.
Ethylamino-acetocatechol, 149.
Ethylamino-ethylcatechol, 149.
Ethyl antimonyl tartrate, 216.
— bromide, 50, **51**.
— chloride, 50, **51**.
Ethylene-chlorhydrin, 102, 103.
Ethylene-dibromide, 51.
Ethylene-diethyl sulphone, 60.
Ethyl ether, 51, 55.
Ethylidene diethyl sulphone, 60.
— dimethyl sulphone, 60.
Ethylmorphine, 109, 110.
N-Ethyl-phenacetin, 73.
(di)-Ethyl pinacone, 59.
α Ethyl piperidine, 80.
Ethyl-propyl-malonyl urea, 57.
Ethyl salicylate, 162.
— urethane, 46, 47, **58**.
Eubornyl, 189.
α-Eucaine, **96**, **97**, 134.
β-Eucaine, **97**, **98**, 134.
— lactate, 97.
Eucodeine, 110.
Eucol, 167.
Eugenol, 162.
iso-Eugenol, 167.
Eugenol carbonate, 166.
— methyl ether, 141.
Euphorin, 69, 75.
Eupyrin, 76.
Euquinine, 84.
Euresol, 153.
Europhen, 184.
Eusol, 179.
Exalgin, 69.
Exodin, 227.

Ferripyrin, 195.
Fibrolysin, 239.
Flavine derivatives, 173-174.
Flavopurpurin, 226.
Formaldehyde, 15, **175**, 176, 177.
Formamint, 176.
Formanilide, 68.
Formurol, 177.
Fortoïn, 231.
Fowler's solution, 197.
Frangulin, **226**, 232.
Fumaric acid, 33, 34.

GALLACETOPHENONE, **41**.
Gallic acid, 177.
Galyl, 212.
Gentisinic acid, 40.
Glucosides, 1, **232**.
Glutol, 175.
Glycerol, 21, 162.
— esters of, with salicylic acid, etc., 162.
Glycerophosphoric acid, 236-237.
Glyceryl ether, 22.
Glycine, 42, 43.
Glycosal, 162.
Glycuronic acid derivatives, 40, 41, 42.
Grey oil, 191.
Griserin, 186.
Guaiacetin, 169.
Guaiacol, 20, 155, **164-165**.
— cacodylate, 167, 203.
— carbonate, 165.
— carboxylic acid, 169.
— esters of, 167.
— phosphite, 167.
Guaiamar, 164.
Guaiaperol, 168.
Guaiathol, 165.
Guanidine, 26.
Gynoval, 236.

"H"-ACID, 172.
Hæmatogen, 196.
Hæmoglobin, 195.
Hæmol, 195.
Halazone, 181.
Halogen in organic compounds, effect of, 23.
Hectine, 208.
Hedonal, 58.
Helmitol, 177, 223.
Hemisine, 136 (see also Adrenaline).
Hermophenyl, 193.
Heroin, 110 (see also Diacetyl-morphine).
Hetocresol, 159.
Hetol, 159, 203, 217.
Hexamecoll, 169, 176.
Hexamethylenetetramine, **176-177**, 222-223.
Hexamine, 176, 177.
Hexaminoarsenobenzene, 213.
Hexylamine, 1[illegible]7.
Hippuric acid, 42, 220.
Histamine, 139.
Histidine, 138.
Holocaine, 98.
Homatropine, 90.
Homogentisinic acid, 40.
Homoprotocatechuic acid, 120.
Homoveratraldehyde, 141.
Homoveratric acid, 120.
Homoveratroyl chloride, 119-120
Hordenine, **144**, 148.
— methiodide, 144, 148, 150.
Hydracetin, 67.
Hydrargol, 192.
Hydrargotin, 193.
Hydrargyrol, 193.
Hydrastine, 116, **123**, 126.
Hydrastinine, 126, 127.
Hydrazine, 8, 26.
Hydrazoic acid, 26.
Hydrocarbons, action of, 17.
Hydrocyanic acid, 15.
Hydrogen peroxide, 190.
Hydropyrin, 157.
Hydroquinone, 39, 162.
p-Hydroxy-*ω*-amino-acetophenone, 143, 144.
m- and *p*-Hydroxybenzoic acids, 156.
o-Hydroxybenzoic acid (see Salicylic acid).
m-Hydroxy-benzoyl-tropeine, 89.
p-Hydroxy-*ω*-chloro-acetophenone, 144.
Hydroxylamine, 26.
Hydroxyl groups, effect of, 21-23.
p-Hydroxy-phenylacetonitrile, 132.
p-Hydroxy-phenyl-arsenious oxide, 201.
p-Hydroxy-phenyl-arsinic acid, 202, 206, **207**, 209, 210.
p-Hydroxy-phenylethanolamine, 143.
o-Hydroxyphenylethylamine, 149.
p-Hydroxyphenylethylamine, 129, **136**, 137, **138**, **139**, 148.
p-Hydroxyphenylethylethylamine, 145.
p-Hydroxyphenylethylmethylamine, 144-145.
p-Hydroxyphenyl-urethane, 75.
α-Hydroxy-*β*-2-pyridyl-propionyl-tropeine, 89.
Hyoscyamine, 34, 86 (see also Atropine).
Hypnal, 54.
Hypnone (acetophenone), 29, **59**.
— behaviour of in organism, 41.
Hypodermic purgative (see Apocodeine).

ICHTHALBIN, 238.
Ichthoform, 238.
Ichthyol, 238.
β-Iminazolyl-ethylamine, 138.
Indophenol reaction, 72.

Indoxyl, formation of in organism, 39.
Intramine, 239.
Iodalbin, 187.
Iodides, alkaline, 186.
Iodipin, 187.
Iodival, 187.
p-Iodo-aniline, 204.
Iodoform, **181**, **182**-184, 186.
Iodoformal, 182.
Iodoformin, 182.
Iodoglidine, 187.
p-Iodo-guaiacol, 187.
Iodol, 183.
Iodo-lecithin, 238.
Iodolysin, 239.
Iodophenol, 184.
Iodothyrine, 187.
p-Iodoxy-anisole, 185.
Ionization, effect of, 16, 17.
Iron, derivatives of, 195 196.
Isoform, 185.
Isomerism, effect of, 33.
Isomorphous groups, behaviour of, 16.

JALAP, 228.

KAIRINE (hydroxy-N-ethyl-tetrahydro-quinoline), 64.
Kairoline A (N-ethyl-tetrahydro-quinoline, 64.
— B (N-methyl-tetrahydro-quinoline), 64.
Kalmopyrin, 157.
Ketones, effect of, 29, 59.
Kharsivan (see Salvarsan).

LACTOPHENIN, 74.
Lactyl-aminophenol, 164.
Lactyl-aminophenyl-ethyl-carbonate, 77.
"Ladenburg's Rule," 89.
Lambkin's cream, 191.
Laudanine, 105.
Laudanosine, 104, 105, **121**, 126, 127.
Laxin, 228.
Lecithin, 236-237.
Leucine, 137.
Liminal values, 46.
Lithium salts, 220.
Lodal, **127**, 141.
Loew's theory of poisons, 8.
Loretin, 186.
Losophan, 185.
Luargol, 213.
Lutidine, 33.
Lysetol, 222.
Lysidin, 222.
Lysol, 152, 153.

MAGNESIUM-perhydrol, 190.
Malachite green, 172.
Malakin, 76.
Malarin, 76.
Maleic acid, 33, 34.
Malic acid, antimony derivatives of, 216.
Mandelic acid, 89.
Mandelonitrile glucoside, 233.
Maretin, 67.
Martius yellow, 29.
Meconine, 122.
Medinal, 57.
Menthol, 166, 167, **233**, 236.
— carbonate, 166.
— salicylate, 163.
Menthone, 32.
Mercuric chloride, 17, 191.
— cyanide, 17.
Mercurous chloride, 17.
Mercury, colloidal, 192.
— derivatives of, 191-193.
— organic derivatives of, 192-193.
— tannate, 193.
Mesotan, 162.
Metaldehyde, 28.
Methacetin, 70, 73.
Methane, 18, 50.
p-Methoxyphenylethylamine, 139, 145.
p-Methoxyphenyl-trimethylammonium iodide, 145.
Methoxy-quinoline, 63.
Methoxy-tetrahydroquinoline, 63.
Methylacetanilide (see Exalgin).
β-Methyl-adrenaline, 135.
Methylaminoacetocatechol (see Adrenalone).
Methylamino-ethyl-catechol, 149 (see also 3-4-Dihydroxyphenyl-ethyl-methylamine).
α-Methyl-anthraquinone, 225.
N-Methyl-cephaeline, 128.
Methyl-chloride, 24, 50.
Methyl-chloroform, 51.
N-Methyl-emetine, 128.
Methylene blue, 171, 173.
Methylene-citric acid, 177.
Methylenecitrylsalicylic acid, 157
Methylene-dichloride, 24, **50**.
Methylene-diethyl-sulphone 60.
Methylene-dimethyl-sulphone, 60.
Methylene-hippuric acid, 200.
Methyl-ethyl ether, 51.
Methyl-ethyl pinacone, 59.
Methyl-isoeugenol, 134.
2-Methyl-phenomorpholine, 115.
Methyl-phenyl-pyrazolone, 20.

Methyl-pinacone, 59.
N-Methyl-pyrrolidine, 83.
Methylrhodin, 163.
Methyl salicylate, 162.
— — behaviour of in organism, 41 (see also Oil of wintergreen).
N-Methyl triacetone-alkamine, 90, 96.
Methyl-urethane, 46, 47.
N-Methyl-vinyl-diacetone - alkamine, 90, 91.
Meyer's theory of narcosis, 45-46.
Microcidin, 151.
Mitscherlich's law, 16.
Molecular weight, effect of, 33.
Monacetin, 46, 47.
3-Monomethyl-xanthine, 13, 14, 219.
7-Monomethyl-xanthine, 219.
Moore and Roaf's theory of narcosis, 48-49.
Morphigenine, 116.
Morphine, 104, **105-109**, 110-112, 115, 121.
— acyl derivatives of, 109, 110.
Morphine-sulphuric acid, 6, 10, 29.
Morpholine, 112-115.

Naga red, 172.
Naphthalene, 19, 170.
α-Naphthol, 154.
β-Naphthol, 154.
Naphthol-carboxylic acids, 157, 158.
β-Naphthol salicylate, 163.
Naphtholsalol, 163.
Naphthol yellow S, 29.
β-Naphthylamine, 78.
β - Naphthylamine - 3 - 6 - disulphonic acid, 172.
Narceine, 104, **124-125**.
Narcosis, theories of, 44-49.
Narcotine, 104, 105, 116, 117, 121, **122-123**, 127.
— methochloride of, 125.
Nargol, 195.
Neo-kharsivan (see Neo-salvarsan).
Neo-salvarsan, 211-212.
Neurine, 32.
Neurodin, 75.
New bornyval, 236.
New-cacodyl, 203.
New-orthoform, 101.
New-urotropin, 177.
Nicotine, 34, 80, **83**, 148.
Nirvanine, 101.
Nitriles and isonitriles, effect of, 28.
Nitrites, physiological action of, 25.
Nitro and nitroso groups, effect of, 24-25.
Nitro-benzaldehydes, behaviour of in organism, 39.
p-Nitrobenzoic acid, 25, 29.
Nitro-glycerin, 25.
p-Nitrohippuric acid, 25.
Nitro-phenacetol, 115.
o-Nitrophenol, 165.
p-Nitrophenol, 70.
o-Nitrophenylpropiolic acid, 39.
Nitroso-piperazine, 221.
p-Nitrotoluene, 25.
Nizin (see Zinc sulphanilate).
Nosophen, 185.
Novarsenobenzol (see Neo-salvarsan).
Novaspirin, 157.
Novatophan, 224.
Novocaine, 102, 103.

Oil of wintergreen, 162, 166.
Orexin, 229-230.
Orsudan, 205.
Orthin, 67.
Orthoform, 100.
Osmotic permeability, 48.
Overton's theory of narcosis, 45-47.
Oxalic acid, **4**, 33.
Oxynarcotine, 104.

Pæonol, 41.
Papaverine, 104, 105, 116, **117-120**, 121.
— methochloride of, 121.
Paraldehyde, 28.
Paraxanthine, 13, 14, **217-218**.
— 8-amino-, 219.
Parvoline, 33.
Pentabrom-phenol, 154.
Pentachlor-phenol, 154.
Pentamethylene-diamine, 79
Perborax, 190.
Perhydrol, 190.
Peristaltin, 228.
Peronine, 110.
"Pharmacophore," 7.
Phenacetin, [illegible], **70**, 71, 72, 73.
Phenanthrene, 104, 10[illegible], 115.
p-Phenetidine, 70, 71, 72.
— derivatives of, 74-76.
Phenocoll, 76.
Phenol, 21, **152**, 192.
— behaviour of in organism, 40.
— formation from benzene in organism, 39.
Phenolphthalein, 165, 228.
Phenyl-alanine, [illegible]38, 137.
p-Phenylene-diamine, 9.
Phenylethanolamine, 143, 1[illegible]
Phenylethyl alcohol, 145.

Phenylethylamine, 137, 147.
Phenyl-ethyl ketone, 59.
Phenylglycine-arsinic acid, 201, 202, **207**.
Phenylhydrazine, 8.
2-Phenylquinoline-4-carboxylic acid, 223-224.
Phenyl-sulphuric acid, 29, 40, 154.
Phenyl-urethane (see Europhen).
Phesin, 74.
Phloroglucinol, 153-154.
Phosgene, 165.
Phosphatol, 167.
Phosphonium bases, 15, 17.
Phosphorus, action of yellow and red, [illegible]
Phthalic acid, behaviour of in organism, 38.
Phthalimide, behaviour of in organism, 38.
Picoline, 33.
Picric acid, behaviour of in organism, 39.
Picropodophyllin, 228-229.
Pilocarpine, 33, **81**.
iso-Pilocarpine, 33, **81**.
Pinacones, 59.
Pinene, 234, 235.
"Pinene hydrochloride," 234.
Pipecoline, 80.
Piperazine, 220, **221**, 222.
— quinate, 222.
Piperidine, 78, 79, 223.
— tartrate, 223.
Piperidone, 79.
Piperonal, 132, 133.
Podophyllin, 228.
Podophyllinic acid, 228-229.
Podophyllotoxin, 228.
Potassium ferrocyanide, 16.
— sulphocyanide, 28.
Proflavine, 173.
Propion (see Diethyl ketone).
Propylamino-acetocatechol, 149.
Propylamino-ethylcatechol, 140.
Protargol, 19[illegible].
Protocatechuic aldehyde, 132.
— acid, 130.
— — behaviour of in organism, 41.
Protopine, 128.
Protosil, 194.
Prulaurasin, 233.
Purgatin, 227.
Purgatives, 225-229.
Purgatol, 227.
Purgen, 228.
Purpurin, 226.
Purpuroxanthin, 226.
Pyramidon, 6
Pyrantin, 74.
Pyrazole, 64-65.
Pyridine, 33, 78, 106.
— behaviour of in organism, 43.
Pyrogallol, 153.
Pyrrol, 19, 106, 183.
Pyrrolidine, 83.
a-Pyrrolidine, 79.

QUINAFORM, 85.
Quinaphenin, 84, 85.
Quinaphthol, 85.
Quinazoline derivatives, 229-230.
Quinic acid, 219-220.
Quinine, and its derivatives, 81-85.
Quinoline derivatives, 175, 223-224.
Quinone, 39.
Quinotropin, 223.

REACTIVITY, connection between toxicity and, 8.
Resacetophenone, 41.
Resorcinol, 20, 153.
— diacetate, 153.
"Reversed" sulphonal, 60.
Rhamnose, 226.
Rheum (rhubarb), 225.

SACCHARIN, 9, 35, 180.
Safrole, 31.
iso-Safrole, 32.
Salacetol, 163.
Salicin, **159**, 232.
Salicyl-acetic acid, 157.
Salicyl-amide, 164.
Salicyl-anilide, 68.
Salicyl-arsinic acid, 206.
Salicylic acid, 153, 155, **156**, 220.
— behaviour of in organism, 40.
Salicylide, 50.
Salicylosalicylic acid, 157.
Salicyl phenetidine, 75.
Salicyl-tropeine, 89.
Saliformin, 223.
Saligenin, **159**, 220.
Salimenthol, 163.
Salit, 163.
Salocoll, 77.
Salol, 156, **160-162**.
Salophen, 164.
Salvarsan, 202, **210**, 2[illegible].
Sambunigrin, 233.
Scarlet red, 173.
Schmiedeberg's rules on the action of aliphatic compounds, 17.
Senna, 225.
Serum therapy, 170-171.

Sidonal, 222.
Silver compounds, 193-194.
[illegible]amin, 204.
Sodium ferrocyanide, 28.
— hypochlorite, 179.
— nitroprusside, 28.
— phenate, 156.
— phenyl carbonate, 157.
— platinicyanide, 28.
Sodium-salvarsan, 213.
Sodium *p*-toluenesulphonchloramide, 180.
Soluble aspirin, 157.
Solurol, 223.
Solveol, 153, 169.
Somnal, 54.
Somnoform, 50.
Spatial configuration, effect of, 15.
Spirosal, 163.
Stereo-isomerides, action of, 3, 33.
Stibinic acids, 215.
Stovaine, 99
Strophanthidin, 232.
Strophanthin, 232.
Strophanthus, 232.
Strychnine, 12, **81**.
Stypticine, 126.
Styptol, 126.
Subcutin, 102.
Succinylsalicylic acid, 157.
Sulphoform, 239.
Sulphonal, 46, 47, 59, 60, **61**.
p-Sulphondichloramino-benzoic acid, 181.
Sulphones, 59-62.
Sulphonic esters, formation of by organism, 40.
Sulphonium bases, 15, 17.
Sulphur compounds, 238, 239.
Suprarenine, 129, 136 (see also Adrenaline).
Sympathomimetic action, 129, 146.

TANNIC acid, **177**, **178**, 220.
Tannigen, 177.
Tannoform, 177.
Tartar emetic, 197, 216.
Terpenes, 233-235.
Tetrabromcresol, 155.
Tetrachlorphenol, 154.
Tetra-ethylammonium iodide, 147.
Tetrahydro-naphthalene-morpholine, 113, 114.
ac-Tetrahydro-*β*-naphthylamine, 27, 78, 147.
Tetra-iodo-phenolphthaloïn, 185.
Tetra-iodo pyrrol, 183.
Tetronal, 46, 47, **61**.
Thalline, 64.
Thebaine, 103, **108-109**, 1
Theobromine, 13, **217**.
Theocine, 218.
Theophylline, 13, 14, 217, **218**, **219**.
— 8-amino-, 219.
— 8-chloro-, 219.
Thermodin, 75.
Thiocoll, 169.
Thioglycollic acid, antimony derivatives of, 216.
Thiosinamine, 239.
Thymatol, 153, 163.
Thymegol, 193.
Thymin, 223.
Thyminic acid, 223.
Thymol, **153**, 159, 166.
— carbonate, 163.
Thymol-*p*-sulphonic acid, mercury salt of, 192.
Tiodine, 239.
Tolamine, 180.
Toluene, behaviour of in organism, 39.
p-Toluenesulphonchloramide, 180.
p-Toluenesulphondichloramide, 181.
p-Toluenesulphonyl chloride, 180
Toluidine, 68.
— arsenate, 205.
m-Tolylsemicarbazide, 67.
Toxynone, 193.
Traube's theory of narcosis, 48.
Triacetin, 22, 46, 47.
Triacetonamine, 90, 96.
Triacetone-alkamine-carboxylic acid, 97.
Triacetyl-aloïn, 227.
Tribromaloïn, 227.
Tribromphenol, 154.
Tribromsalol, 55.
Trichloracetic acid,
Trichlorphenol, 154.
Trigemin, 54.
Tri-iodo-meta-cresol, 184, 185.
Trimethylamine, 106, 147.
Trimethylamino-acetocatechol chloride, 14[illegible]
Trimethylamino-ethylcatechol chloride, 149.
Trional, 46, 47, 60, **61**, **62**.
Trioxymethylene, 175.
Triphenin, 74.
Triphenylmethane dyes, 171, 172
Triphenyl phosphate, 164.
Triphenylstibine sulphide, 2
Tropacocaine, 88, **94**, 95.
Tropeines, 86, **88**, 89, 94.
[illegible] acid, 86, **87**.

Tropine, 86, 87.
ψ-Tropine, 88, **94**, 95.
Tropinone, 88, **94**, 95.
Truxilline, 93.
Trypaflavine, 173-174.
Trypan blue, 172.
— red, 171, 172.
Trypsin, action of on drugs, 37.
Tylmarin, 160.
Tylnatrin, 157.
Tyramine, 140 (see also *p*-Hydroxyphenylethylamine).
Tyrosine, 12, 30, 137.
— behaviour of in organism, 38.
— ethyl ester, 148.

UNSATURATION, effect of, 31-32.
Uric acid, 219-220.
Urol, 222.
Urosin, 220.
Urotropin, **176**, 219, **222**, 223.
Ursal, 220.
Uvitonic acid, 174-175.

VALERIANIC acids, 24, 186, 236.
— acid derivatives, 236.
Valerobromine, 188.
Validol, 236.
Vanillic acid, behaviour of in organism, 41, **42**.
Vanillin, 118.
— behaviour of in organism, 42.
Veratraldehyde, 119, 126, 133.
Veratric acid, 41, 130.
Veratrole, 20, 168.
Veronal, 56, **57**.
Veronal-sodium, 57.
Vesipyrin, 163.
Vinyl-diacetonamine, 97, 98.
Vinyl-diacetone-alkamine, 90, 97, 98.
Vioform, 186.

XANTHINE, 13.
—derivatives, 13, **217-219**.

ZINC perhydrol, 190.
— sulphanilate, 195.

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GLOSSARY

OF CERTAIN CHEMICAL AND MEDICAL TERMS

MEDICAL.

Analgesic = diminishing pain.

Antipyretic = causing fall of body-temperature in fever.

Hypnotic = sleep producing.

Narcotic = producing marked diminution of mental activity tending to unconsciousness.

Pressor = causing rise of arterial pressure, usually by constriction of the arterioles.

Styptic = checking or arresting bleeding.

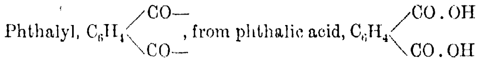
CHEMICAL.

Acyl is a term used to denote an acidic organic radicle derived from an organic acid by removal of the hydroxyl (OH) group from the groups, (—CO—OH) or (—SO_2—OH), containing the acidic hydrogen.

E.g. Acetyl, $CH_3 . CO$—, from acetic acid, $CH_3 . CO . OH$.

Benzoyl, $C_6H_5 . CO$—, from benzoic acid, $C_6H_5 . CO . OH$.

Lactyl, $CH_3 . CH(OH) . CO$—, from lactic acid, $CH_3 . CH(OH) . CO . OH$.



Phthalyl, $C_6H_4\begin{cases} CO— \\ CO— \end{cases}$, from phthalic acid, $C_6H_4\begin{cases} CO . OH \\ CO . OH \end{cases}$

Benzene-sulphonyl, $C_6H_5 . SO_2$—, from benzene-sulphonic acid, $C_6H_5 . SO_2 . OH$.

Alkamine esters have the general formula R—CO—O—$[CR_1R_2]x$—NR_3R_4; they are formed by the esterification of an acid with an alcohol containing an amino-group.

Alkyl is a term used to denote an organic radicle derived from a simple aliphatic hydrocarbon by removal of one hydrogen atom.

E.g. Methyl, CH_3, from methane, CH_4; ethyl, C_2H_5, from ethane, C_2H_6.

Aryl is a term used to denote an organic radicle derived from an aromatic hydrocarbon, by the removal of a hydrogen atom from the aromatic nucleus.

E.g. Phenyl, C_6H_5—, from benzene, C_6H_6; tolyl, $CH_3 . C_6H_4$—, from toluene, $CH_3 . C_6H_5$. Groups such as benzyl, $C_6H_5 . CH_2$—, obtained by removal of a hydrogen atom from the side-chain, must be regarded as mixed alkyl and aryl groups.

CONTENTS

PAGE
PREFACE v
LIST OF ABBREVIATIONS xi
GLOSSARY xii

CHAPTER I

INTRODUCTION—THE THEORY OF THE ACTION OF SYNTHETIC DRUGS 1

CHAPTER II

THE EFFECT OF VARIOUS ELEMENTS AND RADICLES 16

CHAPTER III

THE CHEMICAL CHANGES OF DRUGS IN THE ORGANISM 36

CHAPTER IV

NARCOTICS AND GENERAL ANÆSTHETICS . . . .

CHAPTER V

ANTIPYRETICS AND ANALGESICS. (DERIVATIVES OF ANILINE AND PHENYLHYDRAZINE) 63

CHAPTER VI

ALKALOIDS 78

CHAPTER VII

ATROPINE AND THE TROPEINES—COCAINE AND THE LOCAL ANÆSTHETICS 86

CHAPTER VIII

MORPHINE GROUP AND ISOQUINOLINE GROUPS OF ALKALOIDS 104

CHAPTER IX

PAGE
ADRENALINE AND OTHER DERIVATIVES OF ETHYLAMINE 129

CHAPTER X

DERIVATIVES OF PHENOL (ANTISEPTICS) 152

CHAPTER XI

OTHER ORGANIC ANTISEPTICS, EXCLUDING HALOGEN COMPOUNDS . 170

CHAPTER XII

HALOGEN ANTISEPTICS AND OTHER HALOGEN COMPOUNDS . . . 179

CHAPTER XIII

INORGANIC ANTISEPTICS AND METALLIC COMPOUNDS 190

CHAPTER XIV

ARSENIC AND ANTIMONY COMPOUNDS 197

CHAPTER XV

PURINE DERIVATIVES (DIURETICS) AND OTHER URIC ACID ELIMINANTS 217

CHAPTER XVI

PURGATIVES AND OTHER SUBSTANCES ACTING ON THE GASTRO-INTESTINAL TRACT 225

CHAPTER XVII

VARIOUS OTHER COMPOUNDS OF INTEREST 232

INDEX 241

LIST OF ABBREVIATIONS

USED FOR TITLES OF JOURNALS, ETC.

A. e. P. P.—Archiv für experimentelle Pathologie und Pharmakologie.
Amer. Journ. Pharm.—American Journal of Pharmacy.
Amer. Journ. Physiol.—American Journal of Physiology.
Annalen.—Justus Liebig's Annalen der Chemie.
A. Pharm.—Archiv der Pharmacie.
Apoth. Ztg.—Apotheker-Zeitung.
Beitr. Chem. Physiol. Path.—Hofmeister's Beiträge zur chemischen Physiologie und Pathologie.
Ber.—Berichte der Deutschen chemischen Gesellschaft.
Ber. klin. W.—Berliner klinische Wochenschrift.
Berz. Jahresb.—Berzelius' Jahresbericht über die Fortschritte der Chemie.
B. M. J.—British Medical Journal.
Bul.—Bulletin de la Société chimique de Paris.
Bull. Coll. Agr. Tokyo.—Bulletin of the College of Agriculture, Imperial University, Tokyo.
C. R.—Comptes rendus hebdomadaires de l'Academie des Sciences. (Paris.)
Chemik. Ztg.—Chemiker-Zeitung. (Cothen.)
Deut. med. W.—Deutsche medizinische Wochenschrift.
D. R. P.—Deutsches Reichs Patent.*
E. P.—British Patent.
Fortschr.—Friedländer, Fortschritte der Teerfarbenfabrikation.
J. C. S.—Journal of the Chemical Society (London), Transactions.
Journ. of Physiol.—Journal of Physiology. (London.)
Journ. prakt. Chem.—Journal für praktische Chemie.
Merck's Jahresb.—Merck's Jahresbericht. (Since 1894 an English edition has been published under the title "Merck's Annual Report.")
Monatsh.—Monatshefte für Chemie und verwandte Theile anderer Wissenschaften. (Sitzungsberichte der k. Akademie zu Wien.)
Monatsh. f. pr. Derm.—Monatshefte für praktische Dermatologie.
Münchener med. W.—Münchener medizinische Wochenschrift.
Pflüger's Archiv.—Archiv für die gesammte Physiologie des Menschen und der Thiere, herausgegeben von E. F. W. Pflüger.
Pharm. Ztg.—Pharmazeutische Zeitung.
Proc. Chem. Soc.—Proceedings of the Chemical Society. (London.)
Proc. Amer. Physiol. Soc.—Proceedings of the American Physiological Society.
Proc. Roy. Soc.—Proceedings of the Royal Society. (London.)
Proc. Roy. Soc. Edinb.—Proceedings of the Royal Society of Edinburgh.
Proc. Roy. Soc. Med.—Proceedings of the Royal Society of Medicine. (London.)
Rec. Trav. Chim.—Receuil des travaux chimiques des Pays-Bas et [illegible] Belgique.
Trans. Roy. Soc. Ed.—Transactions of the Royal Society of Edinburgh.
U. S. P.—American Patent.
Zeit. angewd. Chem.—Zeitschrift für angewandte Chemie.
Zeit. physiol. Chem.—Hoppe-Seyler's Zeitschrift für physiologische Chemie.

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* Descriptions of these German patents are given in Friedländer's "Fortschritte der Teerfarbenfabrikation," and abstracts of the more recent ones also in the Journal of the Chemical Society (London) Abstracts, and in the Journal of the Society of Chemical Industry.

CHAPTER I.

INTRODUCTION—THE THEORY OF THE ACTION OF SYNTHETIC DRUGS.

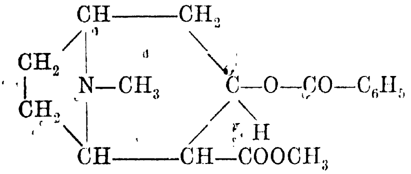
In bygone years Pharmacology was an empirical collection of recipes, hardly deserving the name of a science; but a new era was begun with the investigation of medicinal substances by chemists in the early years of the nineteenth century. These researches soon bore fruit in the isolation of the active principles of many vegetable drugs, and it was found in many cases that the active compound was a nitrogenous substance of basic character, and to this class of substance the name *alkaloid* was given.

Although all vegetable drugs do not contain alkaloids, nevertheless in the majority of cases definite chemical compounds, to the presence of which the action of the drug is due, have been isolated. These non-alkaloidal active principles include a large number of different types of chemical compound, but the class of substances known as glucosides (substances readily hydrolyzed by dilute acids or by enzymes into a sugar and another constituent which is generally physiologically active) is especially well represented.

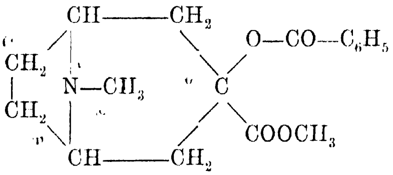
The isolation of the pure active compounds was of very great importance, as it opened up the possibility of an accurate study of the effect of dosage, and, as time went on, enabled quantitative measurements of the physiological effect of the drug to be made. Such progress was obviously impossible as long as investigators were compelled to deal with a crude drug of unknown strength and composition. By this means, also, secondary by-effects, often unpleasant and harmful, could be got rid of in those cases where they were due to the presence of substances other than the desired active principle.

The study of the constitution of the active principles led to attempts at their synthetic production. For a long time, however, synthetic chemistry was not far enough advanced to succeed in the synthesis of such complex substances, and efforts were therefore made to find which portion of the molecule gave rise to the physiological effect in order that simpler analogous compounds might be prepared possessing the characteristic action of the drug.

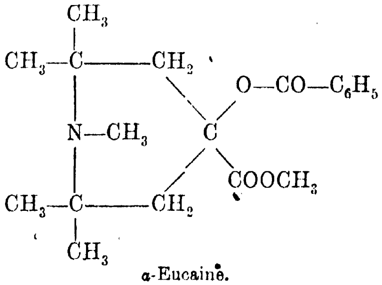
In this way it was found that the physiological action of the drug was in general dependent on its chemical nature, although naturally modified by differences in physical properties, such as solubility, volatility, etc. For instance, certain types of compounds often possess a characteristic action e.g. the quaternary ammonium compounds have a paralytic action on the motor nerves. On the other hand, in the majority of cases the relation between chemical constitution and physiological action is extremely obscure, and is usually to be found only within very narrow limits, outside which any generalizations that may have been made are apt to break down. Thus a very small change in the chemical constitution of a compound is often accompanied by a complete change in its physiological action, as in the case of cocaine, α-cocaine, and α-eucaine,



Cocaine.



α-Cocaine.



α-Eucaine.

the first of which has a strong local anæsthetic action, whilst the second has no local anæsthetic action whatever, and the third—which resembles α-cocaine in its chemical constitution more than it does cocaine—has a marked local anæsthetic action, just like cocaine itself. In this connection mention should be made of the fact that a very considerable difference in physiological action is often shown by stereo-isomerides, as in the case of *d*- and *l*-nicotine, *d*- and *l*-hyoscyamine, pilocarpine, and isopilocarpine, etc.

At this point it may be advisable to indicate the relation between the chemical composition and the physical properties of a substance. It is held by some pharmacologists that the physiological action of a drug is conditioned solely by its physical properties, but even if this were always the case, it would not exclude a connection between the physiological action and the chemical constitution. It *may* be that the effect of some drugs is due to a subtle combination of various physical properties; these cannot, however, be readily ascertained in the majority of cases, but we can endeavour to correlate the chemical constitution—which is the foundation of these properties—with the physiological action. Another point on which misconception seems to have arisen, is the question of whether a difference in properties between two substances is to be attributed to chemical or purely physical causes. The following quotation from a leading text-book of pharmacology will serve to illustrate this: "Yellow phosphorus, given by the mouth, is a violent poison, but red phosphorus, which only differs from it in its physical properties, is comparatively innocuous. Yet were the two differently constituted chemically, the difference in their action would, no doubt, be referred to this fact." Now, according to all modern views, there is a considerable difference in the chemical constitution of the molecules of the two different kinds of phosphorus, a difference which is manifested in the great difference of their reactivity and of their toxic action. There is probably as great a chemical difference between yellow and red phosphorus as between acetylene, $(CH)_2$, and benzene, $(CH)_6$, but at present we have no means of accurately investigating the molecular complexity of the two solid varieties of phosphorus.

Although the action of some drugs may be conditioned chiefly by their physical properties, yet there are others in which it is undoubtedly due to their chemical character (*e.g.* organic arsenic derivatives certainly owe their trypanocidal and anti-syphilitic action to the presence of the arsenic). The term "chemical " character " rather than " constitution " is used deliberately, as in many cases the physiological action of a substance may be traced to some specific chemical property, which is not necessarily closely connected with its constitution. For example, the poisonous character of oxalic acid and its soluble salts could hardly be deduced from its structural formula, but its toxicity is sufficiently explained by the fact that it forms an insoluble calcium salt, a sufficient quantity of calcium in solution being essential for the welfare of the organism.[1] The higher members of this series of dibasic acids, having more soluble calcium salts, are proportionately less toxic. In other cases, however, some kind of relation has been traced between the presence of certain groupings in the molecule and the appearance of certain more or less characteristic physiological effects. These relations may be used in attempting to prepare new synthetic drugs, but it is impossible to forecast the action of *any* new substance with certainty, and careful pharmacological experiments must be made before a new compound can be introduced as a drug.

Many interesting facts concerning the relation between chemical constitution and physiological action are described by Pyman in a lecture to the Chemical Society.[2]

Guidance in our efforts to obtain synthetic drugs may also be obtained from a study of the changes undergone by compounds in the organism. These changes are usually in the direction of the transformation of an active and poisonous substance into a less active and less harmful one. Thus, in order to replace a drug by a new product in which harmful by-effects are eliminated, we can often attain the desired object by studying the changes undergone by the former in the organism, and by taking for the starting-point of the new drug the product of the metabolism of the original drug. For example, it was found that aniline is oxidized by the body into para amino-phenol, and this observation led to the introduction into medicine of a large number of derivatives of para amino-phenol, of which phenacetin is the best-known example. The theories that have been advanced to explain the action of various drugs are chiefly concerned with carbon compounds, as the latter offer practically the only means of comparing substances possessing definite structural relationships with one another. The influence of the chemical constitution of a substance on its physiological effect can be seen from the fact that definite changes in the chemical constitution of substances belonging to the same class, are usually accompanied by definite changes in the physiological effect, and further that the addition of certain molecular groups to differently acting substances can change them into similarly acting or equally inactive bodies. As an instance of this point, mention may be made of the discovery of Crum Brown and Fraser,[1] that various alkaloids possessing the most diverse physiological actions, on combination with alkyl halides to form quaternary ammonium derivatives—

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[1] This accounts for the toxicity of the salts and dilute solutions of the acid; strong solutions of the acid are poisonous in the same way as other n account of their corrosive action.

[2] . 111 (1917), 1103.

$NR_1R_2R_3 + RX = {}^{R}_{X}\!\!>NR_1R_2R_3$, where $R_1R_2R_3$ are organic radicles of any complexity, and RX stands for an alkyl halide, such as methyl iodide, CH_3I, ethyl bromide, C_2H_5Br, etc.—yield substances which in almost every case possess the property of paralysing the motor-nerve endings in the same manner as curare. In this way, by the process of methylation, one can obtain from all tertiary bases ($NR_1R_2R_3$), quaternary ammonium compounds, ${}^{X}_{R}\!\!>NR_1R_2R_3$, which are very, and often disproportionately, poisonous compared with the original bases. Curare itself contains a tertiary base, curine, which is not very poisonous, as well as the far more poisonous ammonium base, curarine. The former on methylation yields the latter, which is 226 times as poisonous as the original substance.

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[1] Crum Brown and Fraser, *Trans. Roy. Soc. Ed.*, 25 (1868), 707; Crum Brown and Fraser, *Proc. Roy. Soc. Ed.*, 6 (1869), 560.

On the other hand, the following examples may be quoted to show that the addition of particular groups to certain substances may weaken or destroy their action. This is well illustrated by the effect of the entrance of acidic groups into the molecule, thus substances containing a hydroxyl group, on combination with sulphuric acid, lose their toxic properties. For instance, phenol is very poisonous, but phenol-sulphuric acid, in the form of its sodium salt, $C_6H_5—O—SO_2—ONa$, is harmless. Morphine, $C_{17}H_{17}NO(OH)_2$, is an extremely powerful and poisonous drug, but morphine-sulphuric acid, $C_{17}H_{17}NO(OH) . O . SO_2 . OH$, is practically inert, and can be given in doses of 5 grams without any harm. This fact should be borne in mind in considering the attempts that are often made of introducing the sulphonic acids of various drugs into medicine, as in nearly every case these are bound to be useless. The effect of introducing the carboxylic acid group ($CO—OH$) is often the same as that of introducing the sulphonic acid group ($—SO_2—OH$). For example, the toxic substance methylamine, $NH_2—CH_3$, is thus changed into the harmless glycine, $NH_2—CH_2—COOH$. The mere addition of acid radicles, such as acetyl, $—CO—CH_3$, without actually converting the substance into an acid may often be sufficient; thus acetamide, $NH_2—CO—CH_3$, is practically harmless, but ammonia, NH_3, is poisonous; acetanilide, $C_6H_5 . NH . CO . CH_3$, is less poisonous than aniline, $C_6H_5 . NH_2$.

An example of an opposite kind is furnished by the effect of the addition of hydrogen to cyclic basis, which is almost invariably to increase their activity, and also their toxic properties. Other examples of this kind will be adduced later, but sufficient have been mentioned to indicate that similar alterations of differently acting compounds often produce similar or identical alterations in the physiological effect.

Ehrlich considers that the selective action of a compound for certain cells depends on the coming together of particular groups in the molecule in some sort of chemical connection with the cell substance. It is only when the compound is held to the tissues ("anchored") by these groups, that the whole complex molecule can take effect and exert its characteristic physiological action. If, therefore, the character of these special "anchoring" groups be altered, the substance can no longer exert its action on these particular cells, but it may happen that the alteration of the "anchoring" group causes the substance to become "anchored" to a different set of cells, and so to produce a different physiological effect. Examples of this type will be quoted subsequently.

These views may be more readily understood by analogy with Witt's theory of dyeing, according to which the colour of a substance is due to the presence of certain "chromophore" groups, such as the azo group, —N = N—, while, for the coloured substance to have dyeing properties, it is necessary for another, salt-forming, group to be present, by which it can be held fast to the fibre. A dye, therefore, must contain both a chromophore group and a salt-forming group, and in the same way, a drug is supposed, besides containing an active group, the "pharmacophore," corresponding to the chromophore, to contain also an anchoring group, corresponding to the salt-forming group.

This analogy may be extended, and the phenomena observed in staining nerve tissues may be compared with the biochemical processes which take place between poisons and the living tissue.

According to Ehrlich, the process of dyeing is similar to that which takes place when a poison is injected into the body. Thus, if a wool fibre be immersed in a dilute solution of picric acid, the colour is withdrawn from the solution and enters the fibre. The fibres of an animal tissue are regarded, in the same way, as withdrawing the dyestuff from the solution, and fixing it, if it is more soluble in them than in the original solution. If the dyestuff is more soluble in another solvent, *e.g.* alcohol, than in the tissue, then the latter can be again decolorized by shaking it in alcohol.

Now, all dyes capable of dyeing nerve cells lose this property if a sulphonic acid group is introduced into the molecule. The bulk of nerve-dyes can be extracted from their aqueous solutions with ether, but the sulphonic acids cannot owing to their greater solubility in water. It is therefore supposed that there are certain substances in the nerve tissues which act like ether does in the test-tube, so that the strong action of certain poisons on the brain and nervous tissues is due to their being extracted in the same way as they can be extracted with ether.

Ehrlich's views have proved to be very stimulating and fruitful, especially in recent years, and some examples of their application are given later in this chapter. Further reference to them will be found in the sections dealing with Antiseptics and Organic Arsenic Compounds (pp. 170-173). A full account would, however, be beyond the scope of this book, and for that the reader is advised to refer to Ehrlich's own writings.[1]

A theory of the action of poisons, in which the subject is regarded from a different point of view, is that due to Loew. It states that all substances which are capable of acting on aldehyde or amino groups, even when in dilute solution, must be poisons for living tissue, on which they will exert a substituting action. The greater the reactivity of a substance for aldehyde (CHO) or amino (NH_2) groups, the greater will be its physiological effect and its toxicity. For example, phenylhydrazine, $C_6H_5 . NH . NH_2$, and hydroxylamine, $NH_2 . OH$, which are so reactive to ketone and aldehyde groups, are strong poisons, both to plants and animals. Aniline, $C_6H_5 . NH_2$, which reacts less readily with aldehydes than does phenylhydrazine, is less poisonous; and similarly ammonia, NH_3, is less poisonous than hydrazine, $H_2N—NH_2$. Substances containing tertiary combined nitrogen are usually less toxic than the corresponding substance where the nitrogen is present in the more reactive form of a secondary imino (NH) group. This is exemplified by the fact that if the hydrogen of the NH group in many alkaloids is replaced by a methyl group the resulting tertiary base is far less poisonous than the original alkaloid. In the same way, if one of the hydrogen atoms of the NH_2 group in aniline is replaced by an alkyl group, the toxicity is diminished, as the substance reacts less readily with aldehydes. A similar explanation is offered of the fact that piperidine is far more toxic than pyridine, and tetrahydroquinoline far more toxic than quinoline, namely, that the

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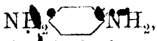
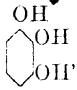
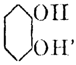
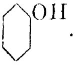
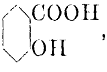
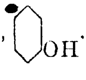
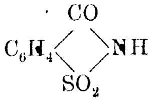
[1] *Deut. med. W.* (1898), p. 1052; *Proc. Roy. Soc.*, 66 (1900), 424; *Zeit. physiol. Chem.*, 47 (1906), 173; "Studies on Immunity," J. Wiley & Sons (1906), 404-42.

[2] "Natürliches System der Giftwirkung," Münich, 1893.

reduced compounds, which contain secondary nitrogen in the place of tertiary, have a greater reactivity with protoplasm. This view is supported by the fact that the toxicity of substances with labile amino groups is increased by the addition of a second amino group, but is lessened when an amino group is changed into an imino, NH, group. Thus, para-phenylene-diamine, , is more toxic than aniline. In general, if the chemical character of a poison is made more labile by any change in the character of the molecule, then it becomes more toxic, and *vice versâ*. An example of this is shown by the hydroxybenzenes, in which the increased reactivity due to the entrance of hydroxyl groups into the benzene ring is accompanied by an increase in the toxicity of the substance. Thus, trihydroxy-benzene, pyrogallol,  is more poisonous than catechol,  which contains only two hydroxyl groups, and this in turn is more poisonous than phenol (monohydroxybenzene), . The labile substance, ammonium sulphocyanide, is toxic to plants, but the more stable isomer, thio-urea, is not. Substances with carbon atoms united by "double bonds" are generally more reactive and more toxic than closely related compounds with simple linkage. Neurine is more poisonous than choline, and other instances of this kind are mentioned in the next chapter. The toxicity of phenols is attributed to their reactivity, especially with aldehydes. This reactivity is diminished by the entrance of acid groups, such as the carboxyl, COOH, and the sulphonic acid group, SO_2—OH, and this diminution in the reactivity is accompanied by a diminution of their toxic power. For example, salicylic acid, , is less poisonous than phenol, . In the same way, saccharin,



is not at all poisonous, as the presence of the carboxyl and the sulphonic acid groups so much diminishes the reactivity of the imino group.

These views of Loew, which are both simple and very suggestive, can nevertheless only be applied to certain groups of substances which react with aldehyde and amino groups They offer no explanation of the selective action of different tissues for various drugs, as they are applied simply to protoplasm, and the protoplasm of any and every tissue has labile aldehyde and amino groups, which, according to this view should react with the drug. Nevertheless, the theory is of value in co-ordinating the action of the various members of certain classes of compounds.

A physical theory of the action of various hypnotics will be discussed in the chapter dealing with the hypnotics.

To return to Ehrlich's theory of "anchoring" groups, many examples may be given to illustrate the application of the theory. In general it is supposed that there are two kinds of groups in the molecule of an active substance, necessary for the action to appear, but in some cases the active group and the anchoring group may be one and the same. If the anchoring group is altered or removed, then a different physiological effect from the original may become apparent if there is present a second possible anchoring group, which can now manifest itself more strongly. As these other anchoring groups may effect different tissues from those affected by the original anchoring groups, so a different physiological effect may be produced, or one of the special physiological effects of the substance may become enhanced. In the first place, the most chemically reactive anchoring group dominates the situation.

For example, morphine has a strong hypnotic effect, and the anchoring group is probably one of the hydroxyl groups. If these are combined with sulphuric acid, then the morphine cannot become "anchored" to the nerve tissues[1] of the central nervous system, and the resulting substance has no effect at all. If the hydroxyl is only altered by the entrance of an organic radicle, with the formation of substances such as methyl, ethyl, or acetyl derivatives, then the hypnotic effect is thrust into the background, while the action on the respiratory centres, produced by morphine to a slight extent, becomes much enhanced and dominates the physiological effect (codeine, heroin, etc.).

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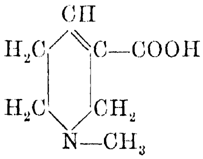
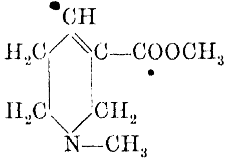
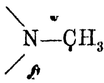
[1] It should be pointed out that the loss of the physiological activity of morphine on sulphonation can be accounted for, from the physical point of view, by reason of the change of its solubility. The more soluble substance cannot become "anchored" to the tissues. These two points of view are not, however, antagonistic, and are merely different methods of viewing the same experimental facts.

In those cases where the presence of an acid group prevents the substance from acting on certain tissues in spite of the presence of an anchoring group, the esterification of the acid group causes the physiological action to appear. To illustrate this, the esterifying group must of itself play no part in the physiological effect, which must reside solely in the original substance, and only be hindered from appearing by the presence of the acid group.

For example, arecaidine has no action at all on animals, but arecoline, its methyl ester, is poisonous, and has physiological effects similar to those of pilocarpine and muscarine. The ethyl ester acts similarly to the methyl ester.


Arecaidine.

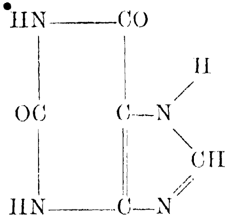

Arecoline.

A precisely similar example is furnished by cocaine, which is the methyl ester of benzoyl-ecgonine. Benzoyl-ecgonine itself is far less active, and is twenty times less toxic than cocaine, owing to the presence of the carboxyl group. It is only when this group is esterified, that the typical action of cocaine appears, and it is immaterial by which alcohol the ester formation is accomplished. In every case the typical action of cocaine appears when the carboxyl group is masked, and therefore it is not the alkyl group which is active, but its presence simply serves to destroy the effect of the group which is inhibiting the characteristic action of the drug. When this group is masked, then the typical "anchoring" group can take effect. Thus it may *possibly* be that for cocaine to act as a local anæsthetic, it must be anchored to the tissues by the  $N-CH_3$ group, or at any rate by some portion of the molecule other than the carboxyl group, but that if a free carboxyl group be present, it becomes anchored by this instead, and so fails to produce its characteristic action.

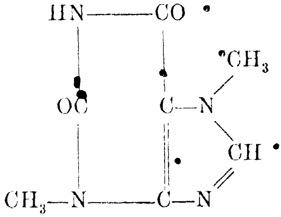
One can thus alter inactive compounds into active ones, or *vice versâ*, or can alter the nature of the action of some compounds by means of a chemical change which alters the group. In this way, if the most prominent property of a drug becomes suspended or diminished, a comparatively masked property becomes developed.

Closely connected with the relation between the constitution and the physiological action of a drug is the second question, of whether there is any connection between the action and the chemical changes which the substance undergoes in the organism. Kobert considers that the strength of the action of a drug is in no way proportional to the amount of the chemical change which it undergoes in the organism. For instance, very active substances, like atropine and strychnine, pass through the body practically unchanged, but an inactive body like tyrosine is completely oxidized by the organism into carbon dioxide and water. Conversely in the case of many compounds, it can be seen that when they have an effect on the body, they have undergone a chemical change. This is also the case with many physiologically active organic compounds, which often show a chemical alteration in the organism. It would therefore seem as if there were no relation between the changes undergone by a drug and its physiological action, but nevertheless some facts can be cited against the view that there is absolutely no connection to be traced.

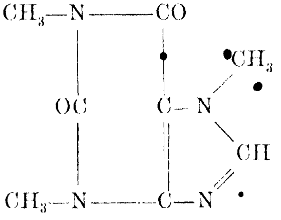
It has been pointed out, in discussing the relation between chemical constitution and physiological action, that *wide* generalizations cannot be drawn, and that it is only in the case of *closely related* compounds that relationships can be traced. In the same way, with regard to the relation between chemical *change* and physiological action, a connection can be found in certain cases of *closely related* compounds. In many cases physiologically active compounds show a degradation of the molecule, and these same substances, if they are made so resistant that they no longer suffer any alteration in the organism, then become inactive. For example, xanthine has no tonic action on the heart muscle, but theobromine (dimethyl-xanthine) has a slight tonic action, and caffeine (tri-methyl-xanthine) has a still more marked tonic action, from which it will be seen that the addition of methyl groups to the nitrogen of xanthine adds a special action on the heart to the ordinary physiological action of xanthine. Experiments, made to ascertain the fate of these compounds in the organism, show that the products of metabolism found in the urine after the administration of caffeine and theobromine contain xanthine bases, poorer in methyl groups than the substances originally administered.



Xanthine.



Theobromine.



Caffeine.

This indicates that the methyl groups have been split off in the organism. In experiments on dogs, caffeine gives first theophylline and then 3-mono-methyl-xanthine, smaller quantities of the two other di-methyl compounds, theobromine and para-xanthine, being also formed.[1] In man it is degraded into theophylline.

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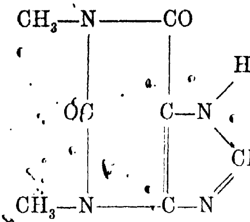
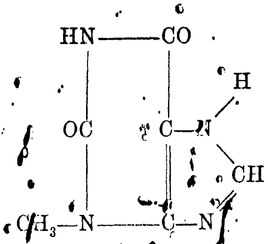
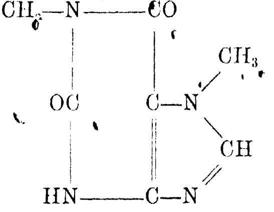
[1] Krüger and Schmid, *Zeit. physiol. Chem.*, 36 (1902), 1.



Theophylline.



3 mono-methyl-xanthine



Para-xanthine.

In both cases, therefore, we have a splitting off of some of the methyl groups, the groups which appear to be responsible for the tonic action on the heart. This case indicates that there is sometimes a relationship between the physiological action and the changes undergone by the substance in the organism. Another well-known instance is afforded by the sulphone derivatives, the hypnotic action of which has been shown to be connected with the presence of ethyl groups in the molecule. The methyl derivatives are inert, and pass through the organism unchanged; the ethyl derivatives produce sleep, and are almost completely decomposed by the organism.

In the case of the alkaloids, it is very difficult in most cases to obtain any knowledge of the mechanism of their action, and generally they seem to pass out of the organism for the most part unchanged. Hence it has been assumed that the action of some of these is "catalytic," an assumption that explains nothing. Another view is that the small portion of the alkaloid that cannot be recovered from the body has undergone a chemical change to which its action is due.

Compared with food-stuffs, most drugs are destroyed by the organism with difficulty, and they owe their activity to this property, but if they are *absolutely* resistant they are quite inactive. Those substances which have a specific action must be fairly resistant, otherwise they would react with *all* protoplasm. In the synthesis of drugs we make use of this property by conferring an artificial resistance on the synthetic substance, so as to prevent it from reacting too suddenly, and also to prevent it from reacting with all tissues, so that it does not show undesirable by-effects. For this reason, all substances which can react with every kind of tissue cannot be used as drugs, unless the reactivity is artificially diminished, or the dose made very small, in which case they can be made useful (*e.g.* formaldehyde, hydrocyanic acid).

In some substances the physiological effect seems to be due more to the stereo-chemical configuration than to the chemical constitution. One general instance will be a sufficient support for this statement. It has already been pointed out that all ammonium bases have a paralytic action on the motor nerves, and that this action is quite independent of the structure of the rest of the molecule. Even the presence of nitrogen is not necessary, as a similar effect is shown in those bases where the nitrogen is replaced by phosphorus, arsenic, or antimony, and it therefore seems that the effect is due to the configuration of the ammonium, phosphonium, or arsonium group, this being a three-dimensional (space) one, while that of the original amines almost certainly lies in one plane. This view is strongly supported by the fact that di-methyl sulphide, $(CH_3)_2S$, and diethyl sulphide, where the sulphur is divalent, and where the configuration *must* lie in one plane, are practically inert, but that tri-methyl sulphonium hydroxide, $(CH_3)_3SOH$, and trimethyl sulphonium iodide resemble the ammonium bases in having a curare-like action on the motor nerves. In these compounds, where the sulphur is tetravalent, its valencies are distributed in three dimensions, as shown by the fact that optically active sulphur compounds of this type have been prepared.[1]

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[1] Smiles, *J. C. S.*, 77 (1900), 1171; Pope and Peachey, *J. C. S.*, 77 (1900), 1073.

CHAPTER II.

THE EFFECT OF VARIOUS ELEMENTS AND RADICLES.

Inorganic Elements.—In 1839 Blake[1] noticed that the action of salts, injected into the blood, depended only on the electro-positive half, and hardly at all on the electro-negative. This is analogous to the action of most esters, which generally resembles that of the alcohol from which they are derived, the explanation in both cases being that acids are usually physiologically inert. Later on[2] it was shown that in any given group of isomorphous substances the action is similar, and is usually increased with increase in atomic weight. This was shown to be the case with Li, Na, Rb, Cs, Ag, Tl; and with Mg, Mn, Co, Ni, Cu, Zn, Cd, and with Ca, Sr, Ba. The only exceptions found were in the case of potassium and ammonium, which differ from the other isomorphous substances of the group. But these salts are also exceptions to Mitscherlich's law that isomorphous substances have similar spectra. It was therefore supposed that physiological action depends on intramolecular vibrations in the same way as the spectra depend on these. The statement made above that isomorphous elements have a similar physiological effect, which becomes stronger with increase in atomic weight, only holds good in the case of electro-positive elements; in the case of negative elements, such as the halogens, there is no relation between physiological effect and atomic weight. Elements forming two series of salts show different effects, according to which class the salt belongs, ferric salts, for instance, differing considerably from ferrous. In many salts the action appears to be due to the ions into which the salt dissociates; for example, potassium ferrocyanide is excreted for the most part unchanged, and has neither the action of a ferrous salt nor of a cyanide, and similarly sodium platinc cyanide, which is found unchanged in the urine, is almost fre from poisonous effects, thus differing both from the cyanide and the platinum salts.

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[1] *C. R.*, **8** (1839), 875; *Proc. Roy. Soc.*, **4** (1841), 155, 284, 285.

[2] *Ber.*, **14** (1881), 394.

The effect of ionization is strikingly indicated by the mercur salts. Mercuric chloride, $HgCl_2$, is ionized and extremel poisonous, but the cyanide, $Hg(CN)_2$, though soluble, is almos non-ionized and is far less poisonous. The insoluble an practically non-ionized mercurous chloride (calomel), $HgCl$ is comparatively non-poisonous.

Phosphonium, arsonium, and stibonium bases do not shov the action of the other phosphorus, arsenic, and antimon compounds. On the contrary, these compounds resemble th substituted ammonium bases, such as those present in curare in having a paralytic action on the motor nerves. In thes cases we do not get the characteristic action of the poisonou elements themselves, but rather one resembling the analogous compounds of the indifferent element nitrogen.

RADICLES AND ELEMENTS IN ORGANIC COMPOUNDS.

Action of Hydrocarbons and Effect of Alkyl Groups.—According to Schmiedeberg[1] the action of aliphatic compounds is governed by the following rules:—

The physiological activity of substances (especially aliphatic) depends chiefly on physical properties. The readiness with which a substance is absorbed is a very important point, as obviously a substance that is not absorbed can have no action on the system. Volatility and solubility in water are of great importance, a fact which is illustrated by the paraffin series, the lower and more volatile members of which show the characteristic narcotic effect of the hydrocarbon groups, while the insoluble non-volatile higher paraffins are without any action at all.

The following rules show the effect of substituent alkyl groups:—

(1) Very poisonous radicles, on substitution by simple alkyl groups, lose the intensity of the original character of the group.

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[1] *A. e. P. P.*, 20 (1886), 201.

For example, by substituting alkyl radicles for the hydrogen of HCN, the nitriles, RCN, and isonitriles, $R—N \equiv C$, are obtained, and only become poisonous when HCN is split off in the organism. Also cacodyl oxide, $(CH_3)_2As—O—As(CH_3)_2$, where the oxygen of arsenious oxide is replaced by two methyl groups, does not show the characteristic arsenic effect until after it has begun to decompose in the body.

(2) On the other hand, the effect of the alkyl groups can be lessened or altogether lost by combination with other atoms or groups. For instance, the amines of the fatty series (*e.g.* mono-, di-, and tri-methylamines) behave like ammonia and have no narcotic action. Nevertheless, the first rule holds in this case as well, as these amines are less toxic than ammonia.

(3) When a compound is formed by the union of two groups through an oxygen atom, then the physiological effect depends upon the nature of the two components, each of which acts independently of the other. In those cases where both parts of the compound are similar or equivalent alkyl groups, as in the case of the simple and mixed ethers, then the action of the whole compound is a simple one, and these substances resemble the corresponding alcohols in their physiological effect. To this class of substances should be added those esters the acids of which yield neutral (sodium) salts without any specific physiological action. For this reason, acetic ester and its homologues are classed with the alcohols. If, on the contrary, the acid has a specific action of its own, then this becomes apparent in the ester, and exerts a modifying influence on the physiological effect of the alkyl group—*e.g.* amyl nitrite.

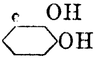
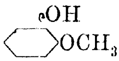
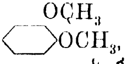
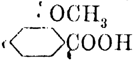
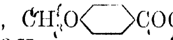
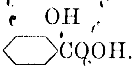
These rules of Schmiedeberg are of value, not only in summarizing the effect of alkyl groups, but, as can be seen above, are also useful as applied to other groups of substances, especially the ethers and the alcohols, the effect of which is due to the alkyl groups contained in them.

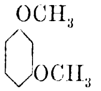
The hydrocarbons of the methane series are, as would be expected from their chemical nature, less active physiologically than those of the ethylene, acetylene, or benzene series. The lower members, when inhaled, produce anæsthesia and sleep, and in larger quantities asphyxiation. The toxicity and the strength of the narcotic action increase as the series is ascended, but on further ascending the series, the action diminishes owing to their diminished volatility and solubility, so that the higher members are quite inert. The members of the ethylene series have a similar narcotic action; amylene, C_5H_{10}, resembles chloroform in its narcotic properties.

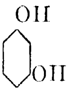
The benzene hydrocarbons have a paralysing action on the motor nerves, and a more noteworthy action on the brain and cord, causing lethargy and somnolence. Bromobenzene and chlorobenzene act in the same way as benzene itself. Naphthalene, $C_{10}H_8$, is less toxic than benzene, but slows the respiration and, in fever, lowers the temperature. It also has the property of decreasing nitrogen metabolism. Diphenyl is physiologically inert, while thiophene, furfurane and pyrrol resemble benzene to a certain extent.

Effect of Alkyl Groups.—Some of the effects of introducing alkyl groups into a compound have already been mentioned in connection with Schmiedeberg's rules, but there are many different effects to which attention may be given. The convulsive properties of ammonia are diminished by the entrance of methyl groups, trimethylamine being free from these effects. In aniline, replacement of the hydrogen of the amino group causes diminution of the convulsive properties as with ammonia, but replacement of the hydrogen of the nucleus by methyl groups causes an increase in these effects. The marked influence of the entrance of methyl groups into the xanthine molecule has already been pointed out. The foregoing examples show that the addition of a methyl group to a nitrogen atom can produce very diverse effects, and a similar variety can be found in the effect of the methylation of an hydroxyl group. The alkyl ethers of the type R . O . R, where R represents an aliphatic hydrocarbon radicle, are distinguished by their resistance towards oxidation, and physiologically they show a marked hypnotic action, as in the case of ordinary ethyl ether, $C_2H_5—O—C_2H_5$. This hypnotic action is also shown by many other compounds containing an ethoxy group, $—O—C_2H_5$, such as ethoxy-caffeine.

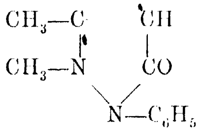
In many cases, replacement of the hydrogen of an hydroxyl group by a methyl group diminishes the physiological activity.

For instance, catechol, , is more poisonous than guaiacol, , and this in turn is more poisonous than veratrole, , and ortho-methoxy-benzoic acid, , and anisic acid, , are less active than salicylic acid, . On the other hand, in some cases the activity of a compound is increased by the methylation of an hydroxyl group. For instance, di-methyl-resorcinol is extremely poisonous, far more so than resorcinol—

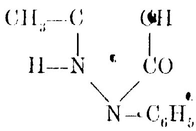




In some cases, the methylation of a hydroxyl, and even more often of a carboxyl group, may cause a very marked change in the physiological action of a compound, owing to the methylation producing a new anchoring group for the molecule. It has already been pointed out how the entrance of an alkyl group into certain acids often causes the full appearance of certain previously masked properties, as in the case of cocaine, arecoline, etc. Possibly a similar explanation may be given of the antipyretic action of phenyl-dimethyl-pyrazolone (antipyrine), phenyl-methyl-pyrazolone being inert.



Phenyl-dimethyl-pyrazolone (antipyrine).



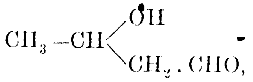
Phenyl-methyl pyrazolone.

In the chapter on hypnotics, reference is made to the importance of ethyl groups in the hypnotic ketones and sulphones, in which compounds the ethyl groups seem to have a marked influence in causing the hypnotic character to appear, whereas methyl groups are entirely without this influence. In fact, there appears to be a marked difference between the ethyl and methyl groups with respect to their action on the central nervous system, for which the former seem to have a special affinity. Other groups of compounds show similar relationships. An interesting experimental result points to the same conclusion, as it has been shown that certain dyes containing the diethyl-amino group, $N(C_2H_5)_2$, possess the property of dyeing the nerve fibres, but the corresponding dyes containing the dimethyl-amino group, $N(CH_3)_2$, do not have this property (Ehrlich and Michaelis).

Another example of the difference between methyl and ethyl groups is furnished by para-phenetol-carbamide, $C_2H_5O . C_6H_4 . NH . CO . NH_2$ (Dulcin), which is two hundred times sweeter than sugar, whilst the corresponding methyl derivative, $CH_3O . C_6H_4—NH—CO—NH_2$, is tasteless.

The entrance of a phenyl group often produces a marked change in the physiological action of a compound, but the effect varies greatly in different cases, and no general rule can be given.

Effect of Hydroxyl Groups.—The entrance of an hydroxyl group into aliphatic compounds usually produces a weakening of their physiological activity, and this weakening effect is roughly proportional to the number of the hydroxyl groups. For example, the narcotic and poisonous alcohols give rise to the inactive glycols, glycerol, mannitol, etc., and from the very active aldehydes are obtained the less active aldols, such as

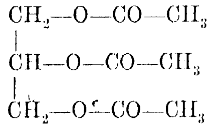


$$CH_3-CH\begin{cases} OH \\ CH_2 . CHO, \end{cases}$$

and by the entry of more hydroxyl groups, the totally inactive aldoses (glucose, etc., $CH_2 . OH(CH . OH)_4 . CHO$). A similar effect is often produced in many other compounds, for example, caffeine, the physiological effect being lost in hydroxy-caffeine.

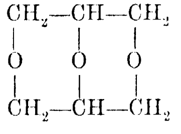
In the aromatic compounds, the entrance of a hydroxyl group usually causes an increase in both the physiological effect and the toxicity. The entrance of a hydroxyl group in benzene itself causes a great increase in the toxicity, together with the appearance of the strong antiseptic properties for which phenol is well known. In the case of a more inert aromatic substance such as benzoic acid, the entrance of a hydroxyl group is again accompanied by an increase in physiological activity, ortho-hydroxy-benzoic acid (salicylic acid) having well-marked antiseptic properties as well as an apparently specific action in rheumatism.

The large number of facts known as to the action of compounds containing a hydroxyl group do not lend themselves to the view that this group has an action of its own, but they point rather to the fact that it very often performs the function of an "anchoring" group. The modification of such groups by esterification or alkylation neutralizes or alters the effect of these groups in "anchoring" the substance to a particular tissue. If an acyl group enters the hydroxyl group (esterification), then various different effects may be produced. In those cases where the ester is hydrolyzed in the organism, its action is due to that of the original hydroxylic substance, together with that (if any) of the sodium salt of the acid. As the greater number of acids are inert, the action of most esters is due to a delayed action of the alcohol from which they are derived. In some cases, the esters do not appear to be hydrolyzed by the organism, and they then do not behave in the fashion indicated by the foregoing statement. For example, triacetyl glycerol (triacetin)—



$$\begin{array}{l} CH_2\text{—}O\text{—}CO\text{—}CH_3 \\ | \\ CH\text{—}O\text{—}CO\text{—}CH_3 \\ | \\ CH_2\text{—}O\text{—}CO\text{—}CH_3 \end{array}$$

does not show the action of glycerol or of sodium acetate, both of which are practically inert, but possesses a specific action on the nervous system, and is poisonous. Glyceryl ether—



is also an hypnotic, this being an example of the fact that alkyl compounds of this kind, obtained by the addition of an alkyl residue to a hydroxyl group, often show hypnotic properties;

for example, ethoxy-caffeine. In the case of the ethers, such as ordinary ethyl ether, the narcotic properties are strictly in accordance with the close resemblance between the chemical properties of the ethers and the parent hydrocarbons themselves, the narcotic action being simply that of the alkyl groups, as stated by Schmiedeberg in the third of his rules (*loc. cit.*).

Other conditions being equal, primary alcohols are less active than secondary, and these are in turn less active than tertiary. In homologous series, those members with long side chains are in general more active, a rule which also holds for benzene derivatives with side chains. The chief action of ethyl alcohol is on the nervous system, the narcotic effect being preceded by a loss of control of the higher centres, an effect which has led to the mistaken belief that alcohol in small quantities acts as a "stimulant." Although the subject is somewhat controversial, the balance of the pharmacological evidence suggests that there is no justification for the medicinal use of alcohol. An excellent account of modern pharmacological opinion on this subject is given by Cushny in *Science Progress*, No. 8, April, 1908. It is there suggested that if alcohol had been introduced as a modern synthetic remedy, it would probably not have survived more than six months, owing to the fact that any of the desirable effects produced by alcohol can be produced by other drugs with greater certainty. The action of the higher alcohols resembles that of ethyl alcohol, but the intensity increases as the series is ascended.

Effect of Halogen in Organic Compounds.—The most important effect of the entrance of chlorine into the molecule of aliphatic compounds is an increase in their narcotic action, but this useful property is accompanied by an increase in their depressant action on the heart and blood-vessels. Narcotic action and lowering of blood-pressure appear to be general properties of chlorine compounds, and an illustration of the fact that narcotic action, and also the toxicity of chlorine compounds depends upon the amount of chlorine in the substance, is furnished by the chlorine derivatives of glycerine. Glycerol itself is inert, but the chlorhydrins have a narcotic action, and dilate the blood-vessels, this effect being the greatest in the case of trichlorhydrin, $CH_2Cl—CHCl—CH_2Cl$, and least in the case of monochlorhydrin, $CH_2Cl—CH(OH)—CH_2OH$.

This fact is also illustrated by methyl chloride, CH_3Cl, methylene dichloride, CH_2Cl_2, chloroform, $CHCl_3$, and carbon tetrachloride, CCl_4, a series in which increase in the amount of chlorine is accompanied by increased narcotic action and increased toxicity. But in the case of the chlorinated fatty acids, the toxicity decreases with increase of chlorine, trichloracetic acid being practically non-toxic, while monochloracetic acid is strongly poisonous. The chlorinated fatty acids are also anomalous in another respect, as the narcotic action of the sodium salts of the fatty acids increases with rise of molecular weight from acetic acid to valerianic acid, while in the case of the corresponding chlorinated acids it diminishes with increase of molecular weight.

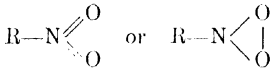
In chloro-caffeine, there is an antagonism between the tonic effect of caffeine on the heart and the depressant action of the chlorine, and it is found that the tonic effect of this substance is less than that of caffeine, but the diuretic effect and the stimulation of the brain due to caffeine are not affected.

The entrance of halogen into the benzene nucleus produces only a slight change in the physiological properties. None of these derivatives have an anæsthetic or hypnotic action, but there is usually an increase in antiseptic power. In general, there is a close resemblance between bromine derivatives and those of chlorine, both in the aliphatic and aromatic series. Organic iodine compounds differ from those of the other halogens in respect of their increased antiseptic power and their diminished hypnotic properties. (Compare chloroform, bromoform, iodoform.) The toxicity of the iodine compounds mark vous eeds that of the analogous chlorine and bromine comp ut this has not seriously hampered their use as antisep a very large number of iodine compounds have been pr this purpose.

Effec and Nitroso Groups.—The entrance of a nitro (N (NO) group in general causes a marked increase hypnotic, this lependently of whether it replaces a hydrogen of this kind, eleus or one in a hydroxyl group.

The ali hydroxyl grou ve rise to dilatation of the blood-vessels, and are therefore used to lower the blood-pressure. The strength of this effect diminishes in descending the series from amyl nitrite to methyl nitrite. All the nitrites act in this manner, the secondary and tertiary being stronger in their action than the primary, probably owing to the fact that they are more readily hydrolyzed to alcohol and nitrite. A similar action is shown by the esters of nitric acid, nitro-glycerin, $CH_2(ONO_2)—CH(ONO_2)—CH_2(O.NO_2)$, and erythrol tetranitrate being largely used in medicine to dilate the blood-vessels.[1]

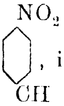
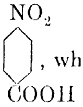
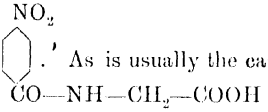
Aliphatic nitro-compounds, such as nitro-methane, which are isomeric with the alkyl nitrites,



$R—O—N=O$

Nitro-compound. Nitrite.

differ from them in their physiological action, being poisonous, but without the property of dilating the blood-vessels.

The entrance of a nitro group into aromatic compounds usually increases the toxicity, nitro-benzene, nitro-naphthol, and nitro-thiophene, for example, all being more poisonous than the substances from which they are directly derived. Paranitrotoluene, , is not very poisonous, because it is oxidized to para-nitro-benzoic acid, , which is then eliminated as para-nitro-hippuric acid, . As is usually the case, the entrance of negative groups diminishes the toxicity, the aromatic nitro-aldehydes being non-poisonous, as they are readily oxidized to the inert nitro-acids.

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[1] The workers employed in explosive factories often suffer from headache caused by the vapour of nitro-glycerine ("N.G." headache).

Effect of Basic Nitrogen Groups.—The entrance of basic nitrogen radicles into aliphatic or aromatic compounds, or the presence of nitrogen in cyclic bases, can produce very important pharmacological effects. The nature of these varies greatly in different cases, and at this point only a few features of interest will be referred to, as the subject will be considered from time to time in the special part of the book.

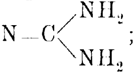
The convulsive action of ammonia and its disappearance on the entrance of alkyl groups has already been referred to. Replacement of the hydrogen of ammonia by acid groups also diminishes the activity of the substance, and produces inert compounds which are found unchanged in the urine.

For example:

Carbamic acid, $NH_2—CO—OH$, is poisonous, probably on account of its unstable character, but its ester (urethane), $NH_2—CO—OC_2H_5$, is more stable and has a hypnotic action.

Hydrazine, $NH_2—NH_2$, is far more toxic than ammonia, but the tetra- and penta-methylene diamines, $NH_2[CH_2]_4NH_2$ and $NH_2[CH_2]_5NH_2$, are quite non-toxic. Hydroxylamine, $NH_2—OH$, is very toxic on account of its reactivity with aldehydes (Loew's theory), and hydrazoic acid and its sodium salt are very toxic. The action of oximes resembles that of the aldehyde from which they are derived together with that of a nitrite, the $=NOH$ group probably being oxidized to a nitrite.

Acetoxime lowers the blood-pressure and has a narcotic action.

Guanidine is toxic, owing to the presence of the labile imino (NH) group,  $HN=C\langle\begin{matrix}NH_2\\NH_2\end{matrix}$; and cyanamide, $CN—NH_2$, has a toxic action similar to that of guanidine.

The salts of the platinum-ammonium bases of the type, $(NH_4)_2PtCl_6$, resemble the other ammonium bases in having a curare-like action.[1]

Very great interest is attached to the experiments that have been made on the effect of the entrance of an amino group into the benzene nucleus, as they form the basis of a large number of antipyretics and analgesics. Amino-benzene

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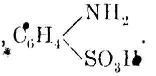
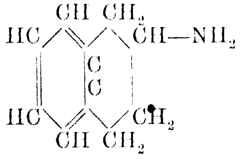
[1] Hofmeister, *A. e. P. P.*, 16 (1883), 393.

(aniline) resembles ammonia in many respects as regards its physiological action, but it also resembles benzene in some of its properties. It causes convulsions, but also paralysis of muscles and nerves, and if one of the hydrogen atoms of the amino group be replaced by an alkyl group, the convulsions no longer appear, but only the paralysing effect remains. If one of the hydrogen atoms in the nucleus of the aniline molecule be replaced by a simple atom, such as bromine, the convulsive effect is retained, and if it is replaced by an alkyl group the effect is increased; but if a complex group, especially an acid group, enters the nucleus, the effect is lost, as for example in amino-benzene-sulphonic acid,  $C_6H_4\begin{matrix}/NH_2\\ \backslash SO_3H\end{matrix}$. Another property of all these derivatives, such as aniline, is that they have a strong toxic action on the blood, forming methæmoglobin. The entrance of a second amino group into the benzene nucleus causes a great increase in the toxicity, all three phenylene-diamines, $C_6H_4(NH_2)_2$, being extremely poisonous.

While all the aromatic derivatives of ammonia and hydrazine possess the property of lowering the temperature of the body, alicyclic-tetrahydro-β-naphthylamine,



produces a marked rise in the body temperature, and an increase in the albumin-metabolism. Substances containing tertiary nitrogen are often only slightly toxic, and are frequently without any effect at all. In many cases, if the tertiary nitrogen is changed into secondary by reduction, powerfully active substances are obtained.

The change of compounds containing tertiary nitrogen into substances with a curare-like action on conversion into ammonium bases has been mentioned in the previous chapter, and will be considered again in connection with the alkaloids.

Effect of the Cyanogen Radicle.—Hydrocyanic acid, HCN, is well known as an exceptionally strong poison, and this fact is probably connected with its great chemical reactivity. The action of cyanogen is similar, but only about one-fifth as powerful. In general, the isocyanides (isonitriles) cause paralysis of the respiratory centre, and the true cyanides (nitriles) produce coma. In this respect, therefore, the behaviour of hydrocyanic acid resembles that of an isocyanide (RNC) rather than that of a true cyanide (RCN). Neither the nitriles nor the isonitriles, however, show the intensely poisonous action of HCN, this only becoming apparent when HCN is again liberated by the organism. The lower members of the series of fatty nitriles, $CH_3—CN$ and $C_2H_5—CN$, are less poisonous than the higher members. Cyanacetic acid, $CN—CH_2—COOH$, is practically non-toxic. Cyanogen chloride, $CN—Cl$, is very poisonous, as it readily yields HCN.

Potassium sulphocyanide, KCNS, is weakly poisonous for warm-blooded animals, but sodium nitroprusside,

$$Na_2Fe(CN)_5NO,$$

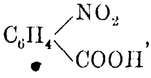
causes death with the appearance of prussic acid poisoning. In sodium ferrocyanide, $Na_4Fe(CN)_6$, neither the iron nor the CN group has any physiological action, and sodium platinicyanide shows no poisonous effect, though the ordinary platinum salts are very poisonous.

Effect of Aldehyde Groups.—The physiological action of aldehydes appears to be closely related to their chemical reactivity. Formaldehyde, $H.CHO$, is very reactive, and has a strong irritant action on the mucous membranes, together with powerful antiseptic properties and a hardening action on the tissues. Acetaldehyde, $CH_3.CHO$, shows the action of the aldehyde group combined with that of the methyl group, as it produces an excitation followed by anæsthesia. The action of its polymeride, paraldehyde, $(C_2H_4O)_3$, is stronger and more continued, and that of the higher polymeride, metaldehyde, $(C_2H_4O)_n$, is more toxic.

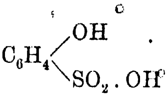
By the entrance of hydroxyl groups into the aldehyde molecule, and also by the condensation of these substances to form aldols, the reactivity of these bodies is appreciably depressed, and so also is their physiological action. The sugars, for example, are physiologically inert. Most of the aromatic aldehydes are of low toxicity, as they are readily oxidized to the corresponding acids, which are usually very inert. It is only in the case of strongly irritant substances that poisonous properties appear, owing to their action on the mucous membrane.

Effect of Ketones.—The ketones in general possess pharmacological properties similar to those which characterize the corresponding alcohols, *i.e.* they have a narcotic action. In the case of the aliphatic ketones this is fairly well marked, on account of the alkyl groups, and a hypnotic action is also shown by the mixed ketones, such as acetophenone, $C_6H_5—CO—CH_3$ (hypnone). A large number of hypnotic substances of a more complex constitution contain a ketonic group, usually together with an ethyl group. These will be discussed in the section dealing with the hypnotics.

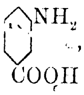
Effect of Acid Groups.—It has already been pointed out how the entrance of acid groups into the molecule causes a marked decrease or a total cessation of the physiological action. Phenol, $C_6H_5—OH$, is poisonous, but phenyl-sulphuric acid, $C_6H_5—O—SO_2—OH$, is harmless. Morphine has a very powerful physiological action and is very poisonous, but morphine-sulphuric acid is quite inactive. In both these cases the diminution of the physiological effect is accompanied by the disappearance of a free hydroxyl group, the hydrogen of which is replaced by the $SO_2—OH$ group. It might therefore be thought that this change is due to the removal of the anchoring group, but the entrance of acid groups has the same effect in many substances where it produces no change in the anchoring or active group. For example, substances containing a nitro group are strongly poisonous, but the entrance of acid groups lowers or destroys the toxicity without altering the nitro group. For example, Martius yellow (dinitro-naphthol) s markedly toxic, but its sulphonic acid (naphthol yellow S) s harmless. Nitrobenzene, $C_6H_5—NO_2$, is poisonous, but nitrobenzoic acid,



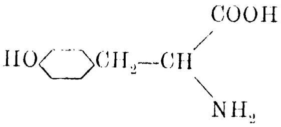
$C_6H_4\begin{cases}NO_2\\COOH\end{cases}$, is harmless. It does not matter whether the sulphonic acid group is united to carbon or to

oxygen, both $C_6H_5—O—SO_2—OH$ and 
$C_6H_4\begin{cases}OH\\SO_2.OH\end{cases}$ being innocuous.

The entrance of carboxyl (COOH) groups into the aromatic nucleus is of great importance from the point of view of the synthesis of drugs, as it generally lowers the toxicity so very much. Benzene itself can be tolerated in doses of eight grams per day, but from twelve to sixteen grams of benzoic acid per day can be eliminated by the organism as hippuric acid, and still larger quantities can be administered without toxic effects, the excess being eliminated unchanged.[1] Aniline, which is more toxic than benzene itself, is rendered practically harmless by the entrance of a carboxyl group, meta-amino-benzoic acid,


, being well tolerated by the organism.

On the other hand, physiological properties which have been lost by the entrance of acid groups can be restored if these groups are esterified. For example, tyrosine,



is not poisonous, but the hydrochloride of its ethyl ester has been shown to be strongly poisonous when administered to dogs.[2]

The addition of acid radicles to active basic substances is of special importance for the preparation of synthetic drugs. This is especially the case with regard to the acetylation of the amino group. By this means, the basicity is weakened and the action of the substance retarded, as it is only after hydrolysis that the active basic portion of the compound becomes free to exhibit its physiological effect. The acid group is usually physiologically inert, and the choice of the particular acid group to be used to combine with the amino group is governed rule, [illegible] by the physical properties of the compound thus formed.

aldols,

and so also

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[1] Nencki, *A. e. P. P.*, 30 (1892), 300.

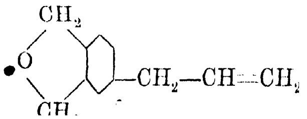
[2] Kohn, *Zeit. physiol. Chem.*, 14 (1890), 189.

Lactyl derivatives are, as a rule, more soluble than acetyl, and these in their turn are more soluble than benzoyl, while salicyl derivatives are usually almost insoluble. Now, in most cases the speed of hydrolysis depends chiefly on the solubility and hence the *rapidity* with which a drug of this type acts depends on the acid group, but the *nature* of the action is usually not affected thereby. Usually, acetyl derivatives are the most convenient, not only because they are the cheapest to prepare, but also because the lactyl derivative is sometimes too rapidly hydrolyzed, whilst the benzoyl derivatives are generally hydrolyzed so slowly that they are excreted largely unchanged, and therefore without having exerted the desired effect. The only one of the previously mentioned acids that has a marked physiological action of its own is salicylic acid, but the salicyl derivatives of basic compounds are so insoluble that they usually escape from the organism almost entirely unchanged, and therefore are therapeutically useless.

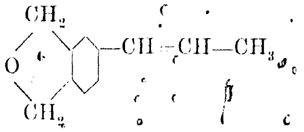
The presence of the benzoyl group is of great importance in a large number of substances, especially in some of the alkaloids. Ecgonine methyl-ester is without any noteworthy action, but its benzoyl derivative, cocaine, has a very important physiological action, producing local anaesthesia and other powerful effects. These facts are discussed in another section, so need not be enlarged upon at present.

Effect of Unsaturated Linkages. — Unsaturated compounds are usually far more toxic than the corresponding saturated ones, a fact which is in accordance with their greater chemical reactivity. For example, propyl alcohol, $CH_3—CH_2—CH_2—OH$, is a narcotic, and causes intoxication, but is not really poisonous, whereas allyl alcohol, $CH_2=CH—CH_2—OH$, has strong poisonous properties, but is without the narcotic action which is characteristic of the saturated alcohols. Indeed, the unsaturated alcohols are distinguished by their highly poisonous character.

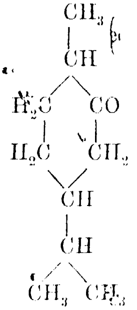
Safrole,



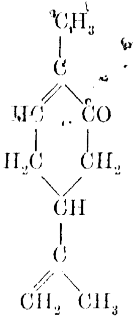
is far more poisonous than any other ethereal oil that has been experimented upon, and the isomeric compound, iso-safrole,



is also poisonous, but not so strongly as safrol. Menthone is far



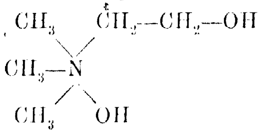
Menthone.



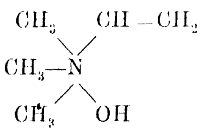
Carvone.

less toxic than carvone, which differs from it only in containing two unsaturated linkages, and acrolein, $CH_2=CH—CHO$, and crotonic aldehyde, $CH_3—CH=CH—CHO$, are far more toxic than the corresponding saturated compounds.

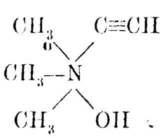
The influence of increasing unsaturation is well illustrated by the following series of compounds :—[1]



Choline (slightly toxic).



Neurine (very toxic).



Far more toxic than neurine.

Allyl-tri-methyl-ammonium hydroxide,

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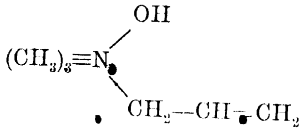
[1] Schmidt, *Annalen*, **267** (1892), 249.



$$(CH_3)_3{\equiv}N\begin{matrix}OH\\ CH_2{-}CH{=}CH_2\end{matrix}$$

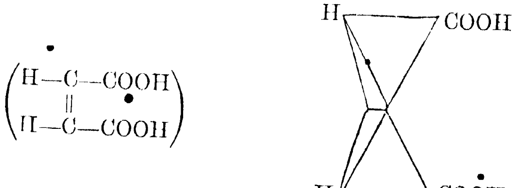
a homologue of neurine, is exceptional in being only slightly poisonous.

Effect of Molecular Weight, Isomerism, etc.—Polymerides often show a different action from that of the original substance, but up to the present no regularities have been observed.

The effect of increasing molecular weight in the series of the paraffins and the alcohols has already been referred to. In the substituted ureas, the narcotic effect increases with the number of carbon atoms in the branched side chain in the same way as it does in the alcohols, and a similar effect is found in the case of the pinacones.

The fatty acids are generally innocuous. Oxalic acid is poisonous, but the toxicity rapidly diminishes as the series is ascended. In the case of the homologues of pyridine, the toxicity increases very rapidly with increase of molecular weight. Pyridine, C_5H_5N, is the weakest in its action, and the intensity of toxic effect increases as the series is ascended through picoline, lutidine, and collidine, to parvoline, $C_5HN(CH_3)_4$, which is eight times as strong in its action as pyridine.

There is often a surprisingly great difference in the activity of stereo-isomerides. Isopilocarpine is probably stereo-isomeric with pilocarpine itself,[1] but it is far weaker in its physiological action. Maleic acid is toxic for dogs, but its stereo-isomeride, fumaric acid, is said to be harmless.[2]



Maleic acid.

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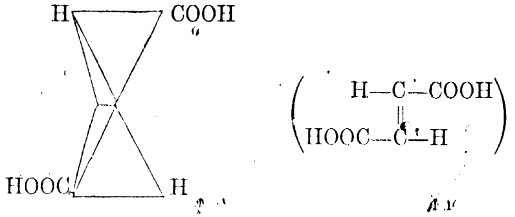
[1] Jowett, *J. C. S.*, **87** (1905), 794.

[2] Ishizuka, *Bull. Coll. Agr. Tokyo*, **2** (1897), 484



$$\left(\begin{array}{c} \text{H—C—COOH} \\ \| \\ \text{HOOC—C—H} \end{array}\right)$$

Fumaric acid

The difference may, however, be due to the different degree of ionization, maleic acid being the more highly ionized of the two.

In the case of stereo-isomerides, which are optically active, marked differences in the physiological action are very often encountered. At this point it will suffice to mention briefly a few examples. Atropine (racemic hyoscyamine) differs in some respects from *laevo*-hyoscyamine,[1] and *laevo*-nicotine is twice as poisonous as the *dextro* variety.[2] One of the most striking examples of this type is that of adrenaline, the natural *laevo* form being about eleven or twelve times as active as the *dextro*.[3] Optical isomerides sometimes show differences in taste or smell, *dextro*-asparagine, for example, being sweet, and *laevo*-asparagine tasteless.[4]

The change in physiological properties which accompanies the change from a plane to a spatial configuration in the case of certain compounds of nitrogen, phosphorus, arsenic, and sulphur, is discussed in Chapters I. and VI.

Differences are often met with in the physiological action of ortho, meta, and para compounds, and in some types of compounds regularities can be traced. It has been suggested that para compounds are more poisonous than ortho,[5] and this is often the case, but in many compounds the reverse is true, ortho nitro-benzaldehyde, for instance, being more toxic than para. In fact, although many differences have been noted between the physiological effects of isomeric benzene derivatives, no general regularities have been traced between the ortho, meta, and para compounds, and between the different tri-substituted derivatives.

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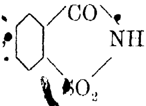
[1] Cushny, *Journ. of Physiol.*, **30** (1904), 193.
[2] Mayor, *Ber.*, **38** (1905), 597.
[3] Cushny, *Journ. of Physiol.*, **38** (1908), 259.
[4] Piutti, *C. R.*, **103** (1886), 134.
[5] Bakorny, *Journ. prakt. Chem.*, **36** (1887), 272.

In this connection it is interesting to note that saccharin, which is an ortho compound,  is five hundred times sweeter than sugar, while the corresponding para compound is tasteless. Some ingenious theories have been advanced to account for the sweet taste of certain compounds, but they are none of them very satisfactory and call for no detailed account.

Closely related isomerides, other than benzene position-isomerides, often show remarkable differences in their physiological action. Cocaine differs from its isomeride α-cocaine only in having a $(.CO.OCH_3)$ group and a $(.O.CO.C_6H_5)$ group on adjacent carbon atoms, while in α-cocaine these groups are on the same carbon atom. Nevertheless, α-cocaine is lacking the characteristic local anæsthetic action of cocaine itself (Chapter VII.).

CHAPTER III.

THE CHEMICAL CHANGES OF DRUGS IN THE ORGANISM.

VERY valuable information can often be obtained by a study of the changes which a substance undergoes in the animal body. By this means an insight into the mode of action of a drug can often be obtained, and a method of preparing and using a less toxic substance can often be devised, owing to the fact that the usual alteration of drugs by the metabolic processes in the organism is in the direction of the conversion of an active and poisonous drug into a less active and less poisonous one. This is usually accomplished by the production of bodies of a more acidic character than the original substance. In some cases this is brought about by a simple process of oxidation, but more often a substance is formed, usually by oxidation but sometimes by reduction, which is then transformed into an inert salt of an acid by means of a synthetic process. The most important of these synthetic processes taking place in the organism are union with sulphuric acid, glycuronic acid or amino-acetic acid. Before considering these synthetic processes, attention must be given to the changes which precede them, by means of which substances are formed which are capable of readily uniting with sulphuric acid, glycuronic acid, etc.

The chemical processes taking place in the organism consist of hydrolytic cleavages (saponification of esters, etc.) in the alimentary canal, and more profound changes of oxidation, and sometimes reduction, in the tissues or blood. In the case of the changes taking place in the alimentary canal, it is found that the saliva acts on but few drugs, owing to the short time that they remain in contact with it, and the fact that only one enzyme—diastase—is present. The contrary is the case in the stomach, in which many drugs can be absorbed, and where unpleasant by-effects are often manifested. For this reason, a great proportion of the work in connection with the synthesis of new drugs consist in modifying previously existing compounds so that they are rendered incapable of being absorbed or of exerting any action in the stomach. The gastric juices contain hydrochloric and other acids, and also an enzyme, pepsin, but it is to their *acid* character that their action on drugs is mostly due. Salts of organic acids are generally decomposed into the free acid and a chloride of the base, but esters and similar compounds are, in the great majority of cases, undecomposed by the gastric contents.

In the small intestine, substances enter an *alkaline* medium and come into contact with the pancreatic enzyme, trypsin. The latter has a marked hydrolyzing action on esters, anilides, and similar bodies, and it is only those substances which are hydrolyzed with great difficulty by all ordinary reagents that escape hydrolysis in the intestine. After saponification in the intestine, the components are able to exert their specific action, and advantage is taken of this fact in preparing derivatives the components of which would exert unpleasant by-effects on the stomach, but which remain undecomposed in that organ, and are then hydrolyzed in the intestine, enabling the components to exert their desired effect.

For example, salicylic acid and its salts often give rise to unpleasant symptoms in the stomach, but acetyl-salicylic acid is comparatively inert and passes through the stomach unchanged. In the intestine it is hydrolyzed into sodium salicylate, which can then exert its useful action, and sodium acetate, which is inert.

Most aliphatic substances are oxidized to carbon dioxide, water, and urea, but there are numerous exceptions. Many substances are oxidized to acids, but aldehydes are never formed by oxidation in the body. On the contrary, aldehydes are often reduced to the corresponding alcohol, chloral, $CCl_3 . CHO$, for example, being reduced to trichlorethyl alcohol, $CCl_3 . CH_2 . OH$.[1] Many substances containing methyl groups are oxidized with difficulty; isopropyl alcohol is said to be partly oxidized to acetone and partly excreted unchanged. Acetone itself is oxidized with difficulty, methyl-ethyl-ketone more readily, while diethyl-ketone is almost completely oxidized.[1] Primary and secondary alcohols are readily oxidized, but tertiary and all halogen-substituted alcohols are difficultly oxidized. Similarly, fatty acids are completely oxidized to carbon dioxide and water, but the chloro-substituted acids are not at all easily oxidized.

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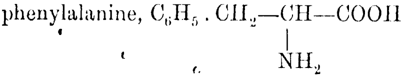
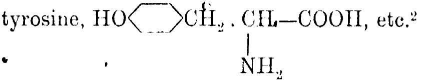
[1] *Zeit. physiol. Chem.*, **6** (1882), 440; *Ber.*, **15** (1882), 1019; *Pflüger's Archiv*, **28** (1882), 506; **33** (1884), 221.

Aromatic compounds are not so readily oxidized by the organism as the aliphatic compounds. In all but a few exceptional cases, the aromatic nucleus remains unchanged, the process of oxidation being confined to the side chains. In those substances which contain a side chain of three carbon atoms, the middle one of which bears an amino group, the substance is completely oxidized. For example—

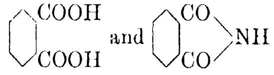


phenylalanine, $C_6H_5 . CH_2—\underset{NH_2}{\underset{|}{C}}H—COOH$



tyrosine, $HO\langle\ \rangle CH_2 . \underset{NH_2}{\underset{|}{C}}H—COOH$, etc.[2]

In dogs also, phthalic acid and phthalimide—



are completely oxidized.[3] Many aromatic compounds are oxidized in the organism by the entrance of a hydroxyl group in the para position to a previously present substituent group, but if the para position is already occupied, no hydroxylation takes place in the animal body. For example, aniline is oxidized to para-aminophenol,[4] $HO\langle\ \rangle NH_2$. Ortho compounds are far more readily oxidized than para or meta. Aldehyde groups are oxidized to carboxyl groups, and in general a substance is usually oxidized to a carboxylic acid if this process takes place at all readily. Toluene, for example, gives benzoic acid, but benzene, on the other hand, is oxidized to phenol.[1] The fate of phenol and similar substances in the organism will be discussed later.

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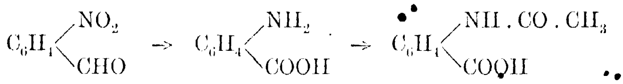
[1] Schwarz, *A. e. P. P.*, **40** (1898), 178.

[2] *Zeit. physiol. Chem.*, **7** (1882), 23; **8** (1883), 63, 65; **10** (1886), 130; **11** (1887), 485; **14** (1890), 189.

[3] Juvalta, *Zeit. physiol. Chem.*, **13** (1889), 26; Mosso, *A. e. P. P.*, **26** (1890), 267.

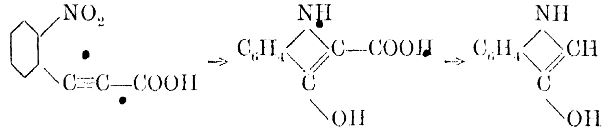
[4] Schmiedeberg, *A. e. P. P.*, **8** (1878), 1.

Reduction of a substance in the organism sometimes takes place, although it is a much more unusual process than oxidation. An interesting example is furnished by chloral, $CCl_3 . CHO$, which is reduced by the organism to trichlorethyl alcohol, $CCl_3 . CH_2 . OH$,[2] a reduction which can only be carried out with extreme difficulty in the laboratory. Quinone is reduced to hydroquinone. Reduction of a nitro group to an amino group is exceptional, nitrobenzene, for instance, never being reduced to aniline, but this type of action sometimes does occur. For example, both meta- and para-nitro-benzaldehydes undergo reduction of the nitro group, accompanied by oxidation of the aldehyde group, the product finally formed by the organism being the acetyl derivative of the corresponding amino acid—[3]



$$C_6H_4\begin{cases}NO_2\\CHO\end{cases} \rightarrow C_6H_4\begin{cases}NH_2\\COOH\end{cases} \rightarrow C_6H_4\begin{cases}NH . CO . CH_3\\COOH\end{cases}$$

Another interesting example of this type of change is furnished by ortho-nitrophenyl-propiolic acid, which is transformed by the organism into indoxyl, this being excreted as potassium-indoxyl-sulphate—[4]



Indoxyl.

Picric acid is partially reduced to dinitro-amino-phenol.

$$C_6H_2(NO_2)_3OH \rightarrow C_6H_2(NO_2)_2NH_2 . OH.^5$$

The final stage in the transformation of drugs into inert substances consists in the formation of acidic substances from the products of oxidation, reduction, etc., by means of the previously mentioned syntheses with sulphuric acid, glycuronic acid, etc. Other synthetic processes sometimes met with are the formation of urea derivatives and sulphocyanides, and more rarely, the introduction of acetyl or methyl groups, and the production of cystine derivatives. Usually no single synthetic process takes place to the exclusion of all others, but, on the contrary, a substance is usually excreted in more than one way, for example, as a glycuronic acid derivative, and also as a sulphonic ester.

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[1] *Dubois Arch.* (1867), 340; *Pflüger's Archiv*, **12** (1876), 148.

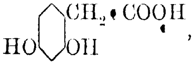
[2] *Zeit. physiol. Chem.*, **6** (1882), 440; *Ber.*, **15** (1882), 1019; *Pflüger's Archiv*, **28** (1882), 506; **33** (1884), 221.

[3] R. Cohn, *Zeit. physiol. Chem.*, **17** (1893), 285; **18** (1894), 123.

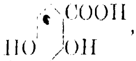
[4] Hoppe-Seyler, *Zeit. physiol. Chem.*, **7** (1882), 178.

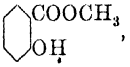
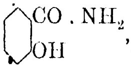
[5] Walko, *A. e. P. P.*, **46** (1901), 181.

Sulphonic Esters.—The sulphuric acid required for these syntheses may be formed by the oxidation of albuminous bodies containing sulphur. It has already been pointed out that phenolic substances are often formed by the oxidation of aromatic compounds, and most of these phenolic compounds are excreted primarily combined with sulphuric acid as alkali salts, and secondarily combined with glycuronic acid. Phenol itself is found in the urine as the sodium salt of phenylsulphuric acid, $C_6H_5 . O . SO_2 . ONa$, a perfectly non-toxic substance. Similar syntheses take place with other hydroxyl derivatives, but if these themselves are non-toxic, they are excreted unchanged without undergoing a synthesis with sulphuric or glycuronic acids. For example, homogentisinic acid,



, which is non-toxic, is eliminated unchanged, but the corresponding gentisinic acid,



, which is toxic, is eliminated partly as the non-toxic sulphuric acid derivative.[1] The entrance of acid groups into phenols, with the corresponding loss of toxicity, destroys the property of combining with sulphuric or glycuronic acids, as in the case of salicylic acid, which is eliminated in combination with amino-acetic acid in the same way as benzoic acid (*i.e.* it forms a compound analogous to hippuric acid).[2] Loss of acid character causes this property of combining with sulphuric acid to reappear, and methyl salicylate, , and salicyl amide, , are found in the urine as sulphuric acid derivatives.[1] Introduction of more hydroxyl groups also causes this property to reappear, as in the case of gentisinic acid, and also protocatechuic and vanillic acids; but veratric

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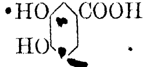
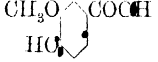
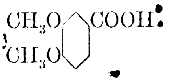
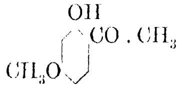
[1] Likhatscheff, *Zeit. physiol. Chem.*, **21** (1896), 422.
[2] See this chapter, last section.

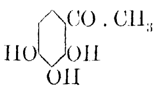

Protocatechuic acid.

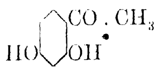

Vanillic acid.


Veratric acid.

acid, which contains no free hydroxyl, does not unite with sulphuric acid. Aromatic ketones are usually oxidized to acids, but if they contain a hydroxyl group the formation of esters with sulphuric or glycuronic acids takes place, to the exclusion of the oxidation of the ketone to the corresponding acid. For example, acetophenone, $C_6H_5 . CO . CH_3$, is oxidized to benzoic acid,[2] but paeonol, gallacetophenone, and resacetophenone are


Paeonol.


Gallacetophenone.


Resacetophenone.

found in the urine as sulphuric and glycuronic acid derivatives.[3]

Glycuronic Acid Derivatives.—This acid, which has the constitution $CHO—(CH . OH)_4—COOH$, is of great interest, as a very large number of poisonous substances are found in the urine as derivatives of it. It seems likely that in the first instance combination takes place between the drug and glucose, the $—CH_2OH$ group of which is then oxidized to $COOH$, with the formation of glycuronic acid. In the case of aliphatic compounds, the resulting compounds are formed with elimination of water, and are probably analogous in structure to the simple glucosides.

For example, chloral is reduced to trichlorethyl alcohol, which then combines with glycuronic acid in the following manner:—

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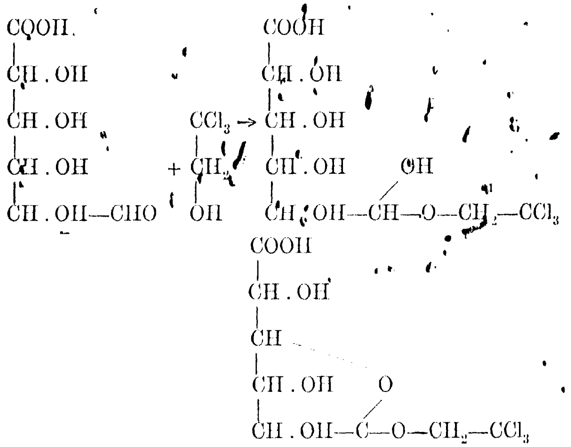
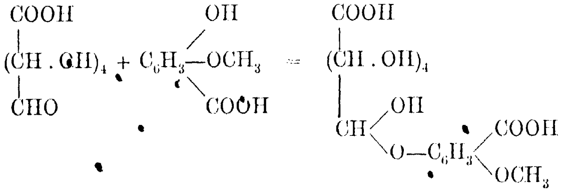
[1] Baumann and Herter, *Zeit. physiol. Chem.*, **1** (1878), 253.
[2] Nencki, *Journ. prakt. Chem.*, **18** (1878), 288.
[3] *Ibid.*, *Ber.*, **27** (1894), 2737.

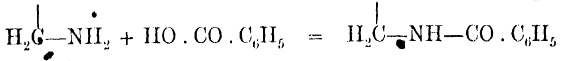


In the case of some aromatic compounds, combination can occur without the elimination of water. For example, it has been shown that vanillin is oxidized to vanillic acid, which then combines with glycuronic acid—[1]



Thymol and carbostyril have been shown to behave in a similar manner.

Derivatives of Amino-Acetic Acid.—Combination between glycine, $NH_2 . CH_2 . COOH$, and benzoic acid takes place in the kidney, with formation of hippuric acid—[2]



$$\begin{array}{c}COOH\\|\\H_2C—NH_2\end{array} + HO . CO . C_6H_5 = \begin{array}{c}COOH\\|\\H_2C—NH—CO . C_6H_5\end{array} + H_2O$$

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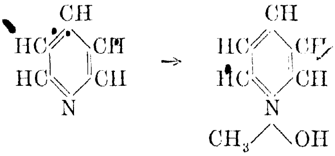
[1] Kotake, *Zeit. physiol. Chem.*, 45 (1905), 320.

[2] Boucis and Ure, *Berzelius' Jahresb.*, 22 (1843), 567.

This synthesis is of great importance, as so many compounds are oxidized in the body to benzoic acid, and it is also typical of a large number of precisely similar syntheses undergone by other carboxylic acids, such as salicylic acid, para-hydroxy-benzoic acid, chloro-, nitro-, and bromo-benzoic acids, anisic acid, naphthoic acid, and many others.

Other synthetic processes that may be mentioned are the formation of the less toxic sulphocyanides from the toxic nitriles,[1] the transformation of pyridine into methyl pyridyl ammonium hydroxide,[2]



and the introduction of an acetyl group into a compound, as in the previously mentioned case of meta-nitro-benzaldehyde, which is transformed into meta-acetyl-amino-benzoic acid.

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[1] *A. e. P. P.*, **34** (1891), 247, 281.

[2] His, *A. e. P. P.*, **22** (1887), 253; R. Cohn, *Zeit. physiol. Chem.*, **18** (1894), 112.

CHAPTER IV.

NARCOTICS AND GENERAL ANÆSTHETICS.

GENERAL THEORIES OF THE ACTION OF NARCOTIC DRUGS.

UP to within quite recent times, the only narcotics in use were the various preparations of opium, and all of these suffered from the great drawback of being dangerous in the doses that were necessary to produce certain sleep, and of sometimes causing unpleasant by-effects. The discovery of many synthetic substances having a powerful narcotic action, and almost free from the dangers and other drawbacks of preparations containing morphine, is one of the great triumphs of the application of synthetic chemistry to pharmacology.

Still more important are those substances which are used as general anæsthetics. These compounds do not differ fundamentally from the other narcotics in their physiological action or chemical constitution, but they are usually volatile substances which are administered by inhalation, so that their effect can be rapidly produced, and the duration easily regulated. On the other hand, for use as a narcotic it is more convenient to employ non-volatile substances capable of offering resistance to oxidation by the organism, and which are therefore slower and more prolonged in their action.

The aliphatic hydrocarbons possess narcotic properties, and these are increased by the introduction of an hydroxyl group to form alcohols. The introduction of more hydroxyl groups, as in glycerol, causes the narcotic action to disappear, the hydroxyl merely playing the part of an "anchoring" group. On the other hand, the narcotic action of many different substances is associated with the presence of alkyl groups, especially ethyl groups. It therefore appears that in the alcohols, the alkyl group, and not the hydroxyl group, is the active portion of the molecule. Replacement of hydrogen atoms in a hydrocarbon by halogen, and especially by chlorine, also greatly increases the narcotic action of the substance, and in these cases the chlorine actually seems to play an important part in the action of the substance, because unlike the case of the alcohols the strength of the action tends to increase with an increase in the number of chlorine atoms in the compound. This narcotic property is characteristic only of the aliphatic halogen compounds; in the case of the halogen derivatives of benzene it is absent.

The inhalation general anæsthetics comprise, therefore, two groups, those in which the action is associated with the presence of halogen in aliphatic combination, and those in which it is associated only with the presence of alkyl groups. The narcotics likewise include substances of these types, and also many compounds, the narcotic action of which seems to be connected with the presence of the carbonyl group (—CO—) in the molecule, and in some cases with the presence of a ring system containing basic nitrogen.

The foregoing statements will show that the anæsthetics and narcotics comprise a number of substances, which, from the chemical point of view, have really very little in common. Attempts have therefore been made to find a relation between some of the physical properties of these substances, and as a result, some interesting facts have been brought to light, which tend to show that in many cases there is a close parallelism between the hypnotic action and certain physical properties of the substance. Not only is this the case, but these physical theories of narcosis are superior to any purely chemical theory that can be devised, in that they throw some light on the mode of action of the hypnotic substances.

This is well illustrated by the work of Overton,[1] and the suggestive theory that has been put forward by Hans Meyer.[2]

It has been shown by Overton that substances may be divided into different groups according to the rapidity with which they diffuse into protoplasm, the rate of diffusion as a general rule depending on the solubility of the substances in fat, lecithin, and "lipoid" substances of that type. If S_f denotes the solubility of a substance in fat, and S_w that of the same substance in water, then the ratio $\frac{S_f}{S_w}$ is called the distribution coefficient of the substance, and according to Overton, the value of this coefficient determines the velocity of diffusion into the cell protoplasm. Now, it was pointed out by Overton and Meyer that anæsthetics and narcotics are generally substances which diffuse rapidly, and therefore these compounds should possess a high distribution coefficient. Meyer compared the aliphatic narcotics, and found that the narcotic power of these was roughly proportional to the magnitude of the distribution coefficient. This fact is sometimes expressed by saying that the strength of the narcotic action of a compound is dependent on its solubility in lipoid substance. This is not strictly true, as it depends not so much on its actual solubility in the lipoid substance as upon the ratio of its solubility in lipoids to that of its solubility in water.

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[1] "Studien über Narkose," Jena, 1901.

[2] Hans Meyer, *A. e. P. P.*, 42 (1901), 103; and 42 (1901), 119 (Baum).

Substance.	Liminal Value.	Distribution-coefficient.	Narcotic Action.
Dimethyl-sulphone-dimethyl-methane[1]		0·106	Very slight.
Diethyl-sulphone-methane[2]		0·151	Slight.
Sulphonal	0·006	1·115	Marked.
Trional	0·0018	4·46	More marked.
Tetronal	0·0013	4·04	,,
Butyl-chloral-hydrate	0·002	1·59	,,
Bromal-hydrate	0·002	0·66	,,
Chloral-hydrate	0·02	0·22	,,
Ethyl-urethane	0·04	0·14	,,
Methyl-urethane	0·4	0·04	,,
Monacetin	0·5	0·06	,,
Diacetin	0·015	0·23	,,
Triacetin	0·010	0·30	,,

Meyer compared the narcotic power of these substances by finding the smallest concentration which would produce a definite physiological effect, and expressed the values as fractions of the normal solution (one gram mol. litre), calling these the

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[1] $(CH_3)_2C(SO_2 . CH_3)_2$.

[2] $CH_2(SO_2 . C_2H_5)_2$.

"liminal values." These "liminal values" can be taken as being approximately inversely proportional to the strength of the narcotic action. On comparing them with the distribution coefficient, it is found that they vary in the opposite direction, being small when the distribution coefficient is large, and these results therefore indicate that the strength of the narcotic action of these substances is approximately proportional to the distribution coefficient.

In the preceding table the substances are arranged together in accordance with their chemical nature, but in order to show the close parallelism of the narcotic effect and the distribution coefficient, it is worth while arranging them in order of magnitude.

Substance.	Distribution-coefficient.	Liminal Value.
Trional	4·46	0·0018
Tetronal	4·04	0·0013
Butyl-chloral-hydrate	1·59	0·002
Sulphonal	1·11	0·006
Bromal-hydrate	0·66	0·002
Triacetin	0·30	0·010
Diacetin	0·23	0·015
Chloral-hydrate	0·22	0·02
Ethyl-urethane	0·14	0·04
Monacetin	0·06	0·05
Methyl-urethane	0·04	0·4

The substances are here given in order of decreasing distribution-coefficient, and it will be seen that with two slight exceptions, the liminal values of the substances, given in the same order, steadily increase. This result is of great interest, especially as the substances tabulated above represent many widely different chemical types. In the case of the sulphone derivatives, a high distribution-coefficient seems to be connected with the presence of ethyl groups, and it had already been pointed out by Baumann and Kast that the narcotic properties of these compounds depended on the ethyl groups. This will be referred to in greater detail in connection with these compounds.

Not only is the theory of Overton and Meyer well supported by the close parallelism shown above, but numerous subsidiary facts appear to give it additional support. One of these is an observation by Mansfeld[1] that some narcotics have a more powerful action when given to starved animals, the explanation suggested being that in these there is less tissue-fat to absorb some of the narcotic, so that a greater portion of the latter is absorbed by the central-nervous system. No doubt, however, an alternative explanation could be offered.

There are nevertheless a good many facts appearing to show that this theory is incomplete and needs some modification, before it can be applied to all cases. For example, the peripheral nerves contain a large amount of "lipoid" substance, but they are much less affected by the aliphatic narcotics.

It has also been pointed out by Cushny[2] that many aromatic compounds have a high distribution-coefficient, but are without narcotic action. A possible explanation of these facts is suggested by the views of Traube, according to which it is the osmotic permeability of a substance which is of primary importance in determining its narcotic action. In support of this view, it is pointed out that pyridine, nicotine, and antipyrine rapidly penetrate the membranes, although their distribution-coefficients are less than unity. Traube considers that surface tension is the force producing osmosis, and he therefore concludes that surface tension and narcotic power should run parallel. This was found to be the case with a large number of narcotics of varied types. It certainly seems reasonable to suppose that rapid penetration of the cells should be the most essential condition for enabling a substance to exert its effect on the interior of those cells. When the substance has once gained an entrance into the cell, its solubility in the cell "lipoids" may be an important factor in determining its narcotic power. The theories of Traube and Overton-Meyer are therefore not altogether antagonistic, and both of them are probably concerned with important facts underlying the mode of action of hypnotic substances.

Moore and Roaf[3] have studied the solubilities of chloroform and certain other anæsthetics in solutions of blood serum and hæmoglobin, and have found them to be considerably higher than in ordinary saline solution or in pure water. The curves connecting the vapour-pressure and concentration of chloroform in serum or hæmoglobin solutions do not correspond to the normal behaviour of a simple solution, but show evidence of association between the solvent and the dissolved substance. Moore and Roaf therefore consider that anæsthetics form unstable compounds or aggregates with the proteins of the tissue cells, which exist only so long as the partial pressure of the anæsthetic in the blood is maintained, and that anæsthesia is due to a paralysis of the chemical activities of the protoplasm as a result of the formation of such aggregations. The curves obtained do not point to the formation of definite chemical compounds, but are more of the nature of adsorption curves.

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[1] Mansfeld, *Centralbl. für Physiol.*, 20 (1906), 664.

[2] "Text-book of Pharmacology," p. 128. 1904.

[3] Moore and Roaf, *Proc. Roy. Soc.*, 73 (1904), 382; *Proc. Roy. Soc. B.*, 77 (1906), 86.

The action of certain substances, such as alcohol, cannot be explained by the foregoing theories. Alcohol is miscible with water in all proportions, and is only slightly soluble in fats, but this need occasion no surprise when it is borne in mind that alcohol does not really belong to the same class of substances as sulphonal and inert bodies of that type, as it exerts some action on proteins and is oxidized in the body. The action of alcohol is, therefore, probably specific, and of a different kind from that of sulphonal, etc.

A theory, according to which narcosis is due to deprivation of oxygen, has been suggested by Baglioni.[1] It is based on the fact that in the case of various aromatic compounds, the paralysing action of the substance is inversely proportional to the amount of oxygen already in the side chain, and that deprivation of oxygen by breathing inert gases, such as carbon dioxide, produces symptoms not unlike those of chloroform narcosis. In support of this view, it might be pointed out that Herter has shown that chloroform, ether, and chloral-hydrate diminish the oxidizing capacity of the tissues. This hypothesis indicates a possible mode of action of the narcotics after they have once entered the cell, the preceding theories indicating the conditions which determine their entrance into the cell substance.

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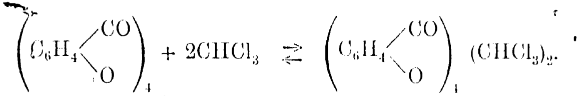
[1] Baglioni, *Zeitschr. allg. Physiologie*, 3 (1903), 313.

Halogen Anæsthetics and Hypnotics.

The most widely used compound of this type is chloroform, which shares with ether the distinction of being the most widely used anæsthetic. The deaths that occasionally take place when chloroform is used may in some cases be due to decomposition products such as phosgene, but it was formerly thought that these were impurities present in the chloroform to start with, and hence methods were devised to purify the chloroform very carefully when it was manufactured. Pictet did this by freezing it and centrifuging away the liquid. Very pure chloroform was prepared by Anschütz by taking advantage of the interesting fact that salicylide (obtained by treating salicylic acid with $POCl_3$ in a neutral solution) forms a crystalline compound with chloroform, giving it up on distillation—



$$\left(C_6H_4\begin{matrix}\diagup CO\\ \diagdown O\end{matrix}\right)_4 + 2CHCl_3 \rightleftarrows \left(C_6H_4\begin{matrix}\diagup CO\\ \diagdown O\end{matrix}\right)_4 (CHCl_3)_2.$$

It has been found, however, that pure chloroform is rapidly decomposed by air and moisture, and this decomposition is best hindered by the addition of about 2 per cent. of ethyl alcohol. Oil of turpentine, thymol, and other substances may also be used for this purpose.

Its anæsthetic action appears to be rendered more certain by the addition of a small quantity of ethyl chloride. Ethyl chloride and ethyl bromide have sometimes been used as anæsthetics, and a mixture of these substances with chloroform has been used, under the name of *Somnoform*, but does not possess any special advantage.

The narcotic action of chloroform is closely connected with the amount of chlorine it contains, the entrance of chlorine into the molecule of many aliphatic compounds conferring narcotic properties upon the substances so formed. This fact is illustrated by the following series of compounds:

CH_4	Methane	Without narcotic effect.
CH_3Cl	Methyl-chloride	Weak ,, ,,
CH_2Cl_2	Methylene-dichloride	Stronger narcotic action.
$CHCl_3$	Chloroform	Strong ,, ,,
CCl_4	Carbon-tetra-chloride	,, ,, ,,

In this series the intensity and the persistence of the action increase with the amount of chlorine. A similar connection can be traced in the derivatives of aldehyde, acetaldehyde, $CH_3 . CHO$, having a slight narcotic action and trichloraldehyde (chloral), $CCl_3 . CHO$, a very strong one.

Although *carbon tetrachloride* appears to have a stronger narcotic action than chloroform, it has no advantage over it, but on the contrary seems to be too toxic for safe use. Its use by barbers to cleanse the hair has led to accidents, at least one fatal case having been recorded. On the other hand, some of the other members of this series have been suggested as substitutes for chloroform; methylene dichloride, CH_2Cl_2, has been recommended, as it produces less vomiting, and methyl-chloroform, $CH_3 . CCl_3$, is said to be less dangerous.

The bromine substitution products of the lower hydrocarbons also have narcotic properties. *Bromoform*, ($CHBr_3$) is sedative, and has been used to suppress attacks of whooping-cough. Ethyl bromide, (C_2H_5Br), has also been used for producing short slight anæsthesia; it is a better anæsthetic and is far less toxic than ethylene-dibromide, the halogen esters of monacid alcohols being generally better anæsthetics and safer than the corresponding esters of diacid alcohols.

Ethyl chloride is used as a general anæsthetic and also as a local one, the latter by spraying it on to the surface to be operated upon. Its use in this case has nothing to do with the presence of chlorine in the molecule, but is due simply to its low boiling-point, the rapid vaporization producing so great a cooling as to cause anæsthesia. Ether is often used in the same way, and methyl-ethyl ether, $CH_3—O—C_2H_5$, which has a very low boiling-point, would be very useful for this purpose as also would be the lower paraffins.

The volatile general anæsthetics are too transient in their action to be used as hypnotics for continued action, but nevertheless, a compound closely related to chloroform has proved very useful for the latter purpose. It was known that *chloral hydrate*, ($CCl_3CH(OH)_2$), is hydrolyzed by alkalies, giving chloroform and alkaline formate, and thinking that a similar action might take place in the body, Liebreich suggested its use as an hypnotic. It was found to possess strong hypnotic properties, but Mering[1] showed that it does not form chloroform in the body, being reduced to trichlorethyl alcohol instead,

$$CCl_3 . CHO \rightarrow CCl_3 . CH_2 . OH.$$

It has been suggested that the action of the halogen narcotics is due to the liberation of free halogen in the body,[2] but there are several facts not in harmony with this view. One of the chief of these is that after administering some of these substances, the amount of alkaline chlorides in the urine is not increased. For example, after taking chloroform, the amount of chloride is increased, but not after taking chloral-hydrate, carbon tetrachloride, and dichloracetic ester, $Cl_2CH—COOC_2H_5$, all of which have an hypnotic action.[3] On the other hand, trichloracetic acid splits off chlorine in the body and has no hypnotic action.

Although chloral hydrate was the first artificial hypnotic to come into general use, it suffers from many drawbacks. Thus, it cannot be injected subcutaneously like morphine, and it has a harmful by-effect on the heart. These drawbacks cannot be got rid of, but attempts have been made to prepare derivatives in which the unpleasant taste and burning feeling in the stomach produced by chloral-hydrate should be absent. All these preparations depend for their use upon the regeneration of chloral itself, as it is found that those which are more stable have no hypnotic action, and therefore all of them must possess the injurious by-effects of chloral itself. For this reason these derivatives of chloral are at a disadvantage compared with the hypnotics of other classes, and they owe their origin rather to the cheapness of chloral and to the fact that it was the first synthetic hypnotic to be brought into use.

Most of these chloral derivatives depend for their production on the reactivity of the aldehyde group in chloral. Condensation products of chloral with oximes have been prepared, but they have not come into practical use. Their formation is in accordance with the general equation—[4]

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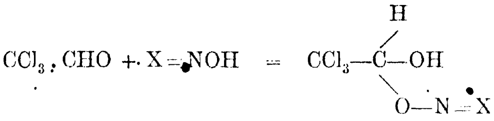
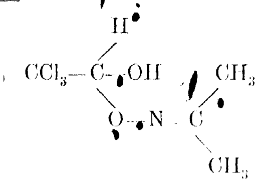
[1] *Zeit. physiol. Chem.*, **6** (1882), 480.
[2] Binz, *A. e. P. P.*, **6** (1882), 310.
[3] Kast, *Zeit. physiol. Chem.*, **11** (1887), 280.
[4] D. R. P., 66,877.

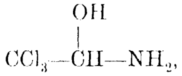


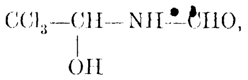
$$CCl_3 . CHO + X=NOH = CCl_3—C(H)(OH)—O—N=X$$

Examples are—



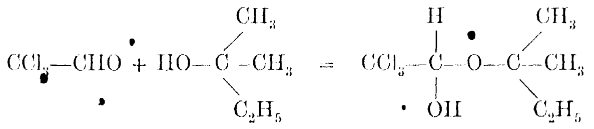
$$CCl_3—C(H)(OH)—O—N=C(CH_3)_2$$

from acetoxime, and similar compounds from nitroso-naphthol, benzaldoxime, camphor-oxime, etc. Other derivatives include those in which the aldehyde group has been combined with basic radicles, *e.g.* chloral-ammonia,  $CCl_3—\overset{OH}{\overset{|}{C}H}—NH_2$, chloral-imide, $CCl_3—CH=NH$, etc.

Chloral-formamide,  $CCl_3—\underset{OH}{\underset{|}{C}H}—NH—CHO$, known as *Chloralamide*, is used as a mild hypnotic and sedative.

Other compounds have been prepared by combining the aldehyde group in different condensations with sugars, but these are not now used in medicine.

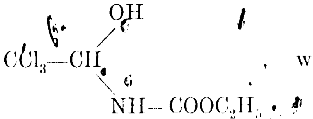
Dormiol is a condensation product of chloral with the hypnotic substance, tertiary amyl alcohol—



$$CCl_3—CHO + HO—C(CH_3)_2—C_2H_5 = CCl_3—C(H)(OH)—O—C(CH_3)_2—C_2H_5$$

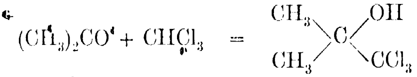
It is a liquid with a burning taste and is insoluble in water. It is as poisonous as chloral, and closely resembles it in its action.

A tasteless solid polymeride of chloral, which possesses strong narcotic properties, has been obtained by the action of aluminium chloride on chloral. Other tasteless compounds have been obtained by combining chloral with orthoform and "new orthoform " (see Chapter VII.). *Hypnal* is formed by the condensation of chloral with antipyrine, but this compound, as well as many others of the same type, has no advantage over a mixture of their components, as they readily split into these, and hence act in the same way as the mixture. The only advantage which can sometimes be claimed for them is that the unpleasant taste of free chloral is masked.

Chloral-urethane,  $CCl_3-CH\begin{cases}OH\\NH-COOC_2H_5\end{cases}$, was first prepared to combine the hypnotic action of chloral with that of urethane. An ethylated derivative of this is soluble in water, and has been given the name of *Somnal*.

Butyl-chloral, CCl_3-CH_2-CHO, has a stronger hypnotic action than chloral, but its effect disappears more rapidly, and its irritant action on the stomach is stronger than that of chloral. *Trigemin* is a compound of butyl-chloral hydrate and pyramidon (see Chapter V.).

Acetone-chloroform (tertiary-trichlor-butyl alcohol), discovered by Willgerodt[1] in 1886, has been introduced into medicine under the name of *Chloretone*. It is prepared by adding potash to a mixture of chloroform and acetone, and is a white crystalline solid, melting at 96-97° C.



$$(CH_3)_2CO + CHCl_3 = \begin{matrix}CH_3\\CH_3\end{matrix}\!>C<\!\begin{matrix}OH\\CCl_3\end{matrix}$$

It has a great advantage over chloral in having no irritant action on the stomach. On the contrary, it has a sedative as well as an anæsthetic action, and very favourable results have attended its use in sea-sickness, vomiting, chorea, etc. It is the chief ingredient in the proprietary medicine known as "Zotos." It also possesses antiseptic powers, for the sake of which it has been occasionally used, and it has sometimes found employment as a local anæsthetic for the mucous membrane of the larynx.

The corresponding bromine compound, $CBr_3 . C(CH_3)_2 . OH$, is known as Brometone, and is also used as a sedative.

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[1] *Ber.*, 19 (1886), 2455.

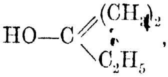
Bromal hydrate, $CBr_3 . CH(OH)_2$, is of no use as an hypnotic, but in large doses it has an anæsthetic action. The corresponding iodine compound, $CI_3 . CH(OH)_2$, is toxic, and affects the muscles and nerve-endings, but has only a slight action on the higher centres, and therefore has practically no hypnotic action.

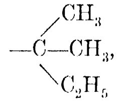
In general, the aromatic halogen compounds have no hypnotic action, but tribromosalol (*Cordal*) appears to be an exception, as it is said to be a good hypnotic.

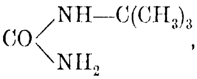
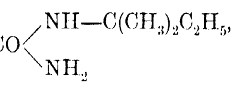
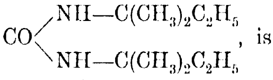
On the other hand, a large number of aliphatic bromine compounds have been brought into use as mild hypnotics and nervous sedatives. These are mostly derivatives of urea or of borneol or valerianic acid, and probably owe their sedative action partly to the presence of the bromine atom, and partly to the organic radicle present. They are described and enumerated in Chapter XII. in the section dealing with bromine compounds (pp. 187-189).

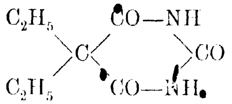
HYPNOTICS, THE ACTION OF WHICH IS CONNECTED WITH THE PRESENCE OF ALKYL GROUPS.

In a large number of compounds the presence of an ethyl group seems to confer upon the substance the power of entering into a close connection with the nervous system. In the case of ethyl alcohol, an excessively large dose is required to produce sleep, but a number of compounds have been discovered which have a hypnotic action in much smaller doses, although their action appears to be due chiefly to the presence of ethyl groups. This difference in their behaviour is probably accounted for by the fact that alcohol is largely oxidized by the tissues, and so only a small fraction of it can produce an hypnotic effect, while these other compounds offer a certain amount of resistance to oxidation, and therefore can exert a more powerful hypnotic action.

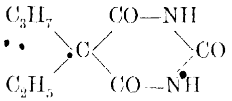
Methyl alcohol has no narcotic action; in the other monohydric fatty alcohols, the narcotic action increases with increasing length of the unbranched side chain. In general, primary alcohols are less active than secondary, and these are less active than tertiary. In the case of tertiary alcohols, the strength of the action depends upon the nature of the radicles attached to the tertiary carbon atom. If the radicle is methyl, the action is relatively weak, but if it is ethyl it is stronger, and the strength increases with the number of ethyl groups. Amylene hydrate,  $HO—C\begin{smallmatrix}(CH_3)_2\\C_2H_5\end{smallmatrix}$, was introduced as a hypnotic in 1887, but the alcohols have not been used as general inhalation anæsthetics, owing to the slight volatility of the higher members, which are the only ones possessing marked narcotic properties. On the other hand, the ethers are far more volatile, and ordinary ethyl ether, $C_2H_5—O—C_2H_5$, is the most widely used general anæsthetic.

If one of the hydrogen atoms in urea be replaced by a tertiary alkyl group, derivatives are obtained possessing a narcotic action. In accordance with the general rule, those containing an ethyl group united to the tertiary carbon atoms have a greater effect than those which contain only methyl groups in this position. For instance, substances containing tertiary amyl,  $—C\begin{smallmatrix}CH_3\\—CH_3\\C_2H_5\end{smallmatrix}$, or tertiary heptyl, $—C(C_2H_5)_3$, are more active than those containing tertiary butyl, $—C(CH_3)_3$.

Tertiary-butyl-urea,  $CO\begin{smallmatrix}NH—C(CH_3)_3\\NH_2\end{smallmatrix}$, produces sleep in doses of 4 grams; tertiary amyl urea,  $CO\begin{smallmatrix}NH—C(CH_3)_2C_2H_5\\NH_2\end{smallmatrix}$, is an excellent hypnotic, which is both more active and more pleasant to take than amylene hydrate. It is, however, slower in its action on account of its smaller solubility. This substance is completely oxidized in the organism, but symmetrical whic. vl-urea,  $CO\begin{smallmatrix}NH—C(CH_3)_2C_2H_5\\NH—C(CH_3)_2C_2H_5\end{smallmatrix}$, is a very stable subfound c. membrane ich passes into the urine unchanged and has no The corresp ction. Tertiary-heptyl-urea is very slightly is known as Brom of 1 gram it produces first intoxication, Besides the urea derivatives already mentioned, many other amides possess hypnotic properties, but most of these are uncertain in their action. Of greater importance are the ureides of dibasic acids (cyclic ureides), many of which have strongly marked sedative properties. Thus, diethyl-malonyl-urea—

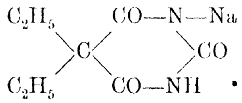


and ethyl-propyl-malonyl urea—

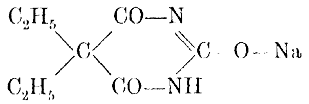


have a strong hypnotic action; whilst dipropyl-malonyl-urea has so intense an hypnotic action that it is too dangerous to be used.

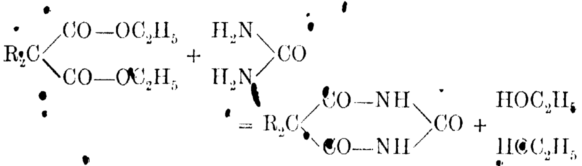
Special mention must be made of *Veronal* (diethyl-malonyl-urea, also known as diethyl barbituric acid and *Barbitone*), which has attained a very great clinical importance, and is now perhaps more widely used than any other synthetic hypnotic. It was formerly supposed to be practically free from toxic properties, but lately several cases of veronal poisoning have occurred. Nevertheless, in the usual doses, it is of very low toxicity and free from harmful by-effects, and has the advantage, compared with most synthetic hypnotics, in the matter of taste, solubility, and promptness of action. Its sodium salt—



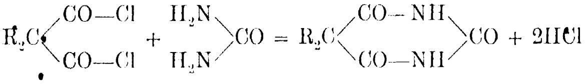
or more likely—



known as *Veronal-Sodium* (*Medinal*), has the valuable property of being extremely soluble (1 in 5) in water. Veronal, which is a white crystalline solid, is prepared by a general method applicable to other di-alkyl barbituric acids. This consists in allowing dialkyl derivatives of malonic-ester to react with urea or alkyl substituted ureas in presence of sodium ethoxide or other metallic ethoxides.[1]

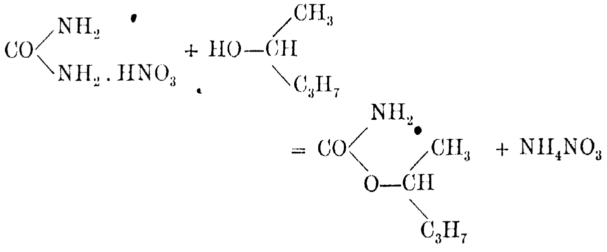


Another method of preparing these compounds is to convert the dialkyl malonic acids into chlorides, and then to heat these with urea.[2]



Instead of using alcoholic sodium ethoxide as a condensing agent in the first process, one can employ the metal sodium itself, or its amide or the dry powdered sodium ethoxide.[3]

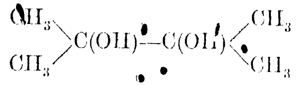
The presence of an alkyl group confers hypnotic properties on many of the urethanes. Ethyl urethane itself, $\mathrm{CO}\left\langle\begin{matrix}\mathrm{NH_2}\\ \mathrm{OC_2H_5}\end{matrix}\right.$, is a mild hypnotic but methyl-propyl-carbinol-urethane, known as *Hedonal*, has a stronger hypnotic action. It is not much used, however. It can be prepared by the action of warm methyl-propyl-carbinol on urea nitrate.



E. Fischer, *Annalen*, **335** (1904), 334 ; Merck, D. R. P., 146,496.
D. R. P., 146,949.
[3] *Ibid.*, 147,278, 147,279, 147,280.

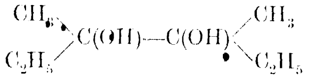
This method can be applied to the preparation of other similar compounds, using various secondary alcohols.[1] The introduction of an acyl group (such as CO—CH_3) into the amino group of the urethanes lessens their toxicity, but does not otherwise alter their physiological action.

The pinacones show a narcotic action, which is least in the case of dimethyl-pinacone—



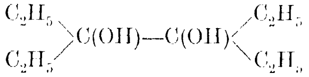
$$\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!C(OH)—C(OH)\!<\!\begin{matrix}CH_3\\CH_3\end{matrix}$$

greater in the case of methyl-ethyl-pinacone—



$$\begin{matrix}CH_3\\C_2H_5\end{matrix}\!>\!C(OH)—C(OH)\!<\!\begin{matrix}CH_3\\C_2H_5\end{matrix}$$

and greatest in the case of diethyl-pinacone—

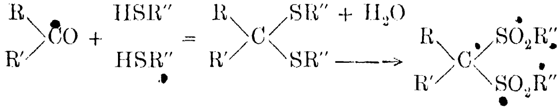


$$\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\!>\!C(OH)—C(OH)\!<\!\begin{matrix}C_2H_5\\C_2H_5\end{matrix}$$

KETONES AND SULPHONES.

Most of the ketones have hypnotic properties. Acetone is somewhat similar in its effect to ethyl alcohol; diethyl-ketone, $(C_2H_5)_2 . CO$ (propion), is a stronger hypnotic and anæsthetic, but its insolubility and unpleasant taste have prevented its extended use. Benzophenone, $(C_6H_5)_2CO$, has a slight hypnotic action, but much less than that of the aliphatic ketones. The mixed aromatic and aliphatic ketones have more marked hypnotic properties in virtue of the aliphatic portion of the molecule, acetophenone (hypnone), C_6H_5—CO—CH_3, being a fairly strong hypnotic, while phenyl-ethyl ketone, C_6H_5—CO . C_2H_5, has a still more powerful action.

Of far greater practical importance are the sulphone derivatives obtained from the ketones by the action of the mercaptans, and subsequent oxidation of the condensation product thus formed—



$$\begin{matrix}R\\R'\end{matrix}\!>\!CO+\begin{matrix}HSR''\\HSR''\end{matrix}=\begin{matrix}R\\R'\end{matrix}\!>\!C\!<\!\begin{matrix}SR''\\SR''\end{matrix}+H_2O\longrightarrow\begin{matrix}R\\R'\end{matrix}\!>\!C\!<\!\begin{matrix}SO_2R''\\SO_2R''\end{matrix}$$

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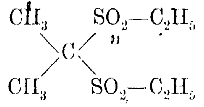
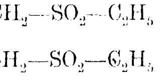
[1] D. R. P., 114,306.

Baumann and Kast discovered that *sulphonal*—

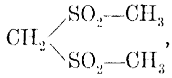


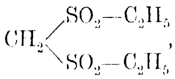
when administered to animals, produced a strong hypnotic effect. A large number of sulphones were then examined by these investigators, who found[1] that di-sulphones in which the sulphone groups are united to two different carbon atoms, are inert; for example, ethylene-diethyl sulphone—

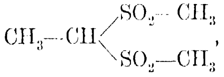


$$\begin{array}{l}CH_2—SO_2—C_2H_5\\ |\\ CH_2—SO_2—C_2H_5\end{array}$$

They also found that sulphones derived from methane (*i.e.* those in which the two SO_2 groups are united to a CH_2 group) are inert, as also are those containing methyl groups but no ethyl groups.

E.g. Methylene-dimethyl-sulphone, , is inactive.

Methylene-diethyl-sulphone, , is inactive.

Ethylidene-dimethyl-sulphone, , is inactive.

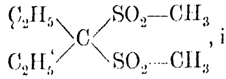
On the other hand, ethylidene-*diethyl*-sulphone—

$$CH_3—CH(SO_2 . C_2H_5)_2$$

has a similar action to that of sulphonal, while the entrance of an *ethyl* group into the central methylene group also brings about the appearance of a narcotic action.

E.g. $C_2H_5—CH(SO_2 . CH_3)_2$, slight narcotic action.

$(C_2H_5)(CH_3)C(SO_2CH_3)_2$,, ,, ,,

, isomeric with, and similar physiological action to, sulphonal ("reversed" sulphonal).

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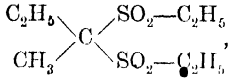
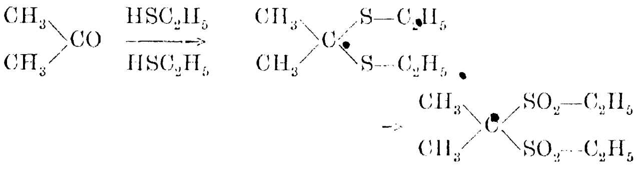
[1] *Zeit. physiol. Chem.*, **14** (1890), 52.

Trional,  $\begin{matrix}C_2H_5\\CH_3\end{matrix}\!>\!C\!<\!\begin{matrix}SO_2-C_2H_5\\SO_2-C_2H_5\end{matrix}$, has a more powerful and prolonged action than sulphonal. *Tetronal*, $(C_2H_5)_2C(SO_2C_2H_5)_2$, is very insoluble, and therefore is not so good an hypnotic, but for dogs it appears to have the most powerful action of all the sulphones.

The above examples indicate that the intensity of the hypnotic action appears to be conditioned by the number of ethyl groups in the molecule. A study of the fate of these compounds in the body has revealed the curious fact that those sulphones which are readily decomposed by ordinary chemical means are relatively stable in the organism, while those which are more resistant to ordinary chemical reagents are oxidized by the organism. For example, sulphonal, "reversed" sulphonal, trional and tetronal, though very stable to strong reagents, such as permanganate, are to a great extent decomposed in the organism, while $CH_2(SO_2 . C_2H_5)_2$, which is easily decomposed by alcoholic potash, is found unaltered in the urine.

Sulphonal and trional are of great practical importance, as they are amongst the most widely used hypnotics. Technically, sulphonal is prepared by the condensation of ethyl mercaptan and acetone in the presence of zinc chloride, and oxidation of the mercaptol thus formed with excess of permanganate.[1]



$$\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!CO \xrightarrow[HSC_2H_5]{HSC_2H_5} \begin{matrix}CH_3\\CH_3\end{matrix}\!>\!C\!<\!\begin{matrix}S-C_2H_5\\S-C_2H_5\end{matrix} \rightarrow \begin{matrix}CH_3\\CH_3\end{matrix}\!>\!C\!<\!\begin{matrix}SO_2-C_2H_5\\SO_2-C_2H_5\end{matrix}$$

Trional is prepared in a similar manner, but the preparation is complicated by the necessity of introducing the extra ethyl group in place of methyl. This can be done in three different ways.[2]

(1) Methyl-ethyl-ketone is condensed with ethyl mercaptan by means of dry HCl, and the resultant mercaptol oxidized.

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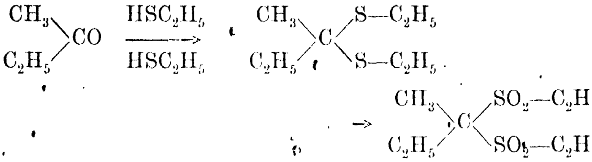
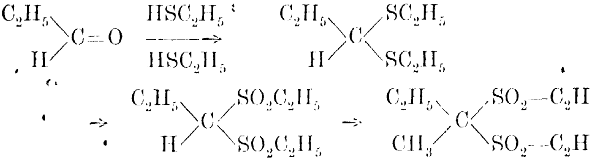
[1] Baumann, *Ber.*, **19** (1886), 2808.

[2] D. R. P., 49,073, 49,366; Fromm, *Annalen*, **253** (1889), 148.

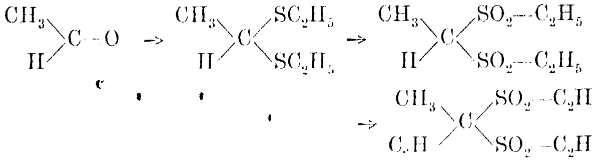


This method is strictly analogous to the method of preparin sulphonal.

(2) Propionic aldehyde is condensed with ethyl mercaptan and the product oxidized as before. The oxidation product i then methylated with methyl iodide and caustic soda to form trional.



(3) By starting with ordinary aldehyde, instead of propioni aldehyde, and ethylating with ethyliodide and sodium ethylat in the last stage instead of methylating, trional can be obtained

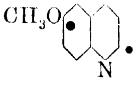


CHAPTER V.

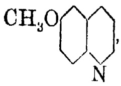
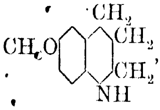
ANTIPYRETICS AND ANALGESICS.

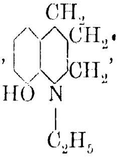
(Derivatives of Aniline and Phenylhydrazine.)

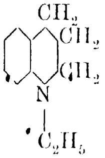
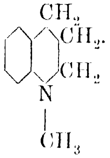
The substances to be dealt with in this chapter include some of the most important of the synthetic drugs. These substances were originally introduced on account of their power of reducing the body temperature in fever (antipyretic action), but their present importance is due, to an even greater extent, to their action on the nervous system in soothing pain (analgesic action).

The original idea of chemists was to produce a compound with properties similar to those of quinine, and this they sought to accomplish by preparing substances the composition of which was closely related to that attributed to that compound. The formula in vogue for quinine was however incorrect, but in spite of this, several compounds were produced which had a marked antipyretic effect, but which lacked one very important attribute of quinine, namely, its specific effect against malaria. Quinine was shown to be a derivative of quinoline, and further to differ from the less active cinchonine in containing a methoxy group in the epi (1-6) position to the quinoline nitrogen, 

Quinoline itself has an antipyretic action, but cannot be used as a drug, owing to its unpleasant by-effects. Paramethoxyquinoline has a weaker antipyretic action than quinoline, but in accordance with the previously mentioned fact that tetrahydroquinoline has a stronger physiological action than quinoline, it was supposed that quinine was a derivative of epi-methoxy-tetrahydroquinoline. This supposition is now known to be incorrect, but nevertheless when 6-methoxyquinoline,

 is reduced to its tetra-hydro compound,  we obtain a substance (*Thalline*) with a strong antipyretic action, though without any specific effect in malaria. It is not used as a drug, as it has harmful effects on the blood and kidneys.

Some earlier experiments had been carried out on *N.-alkyl* quinoline derivatives, and it was found that the introduction of an hydroxyl group caused the effect to appear more rapidly, but also to cease more quickly and suddenly. For example, *kairine*, hydroxy N.-ethyl-tetrahydroquinoline,  is more rapid than *Kairoline* A or *Kairoline* B, which are respectively N.-ethyl-tetrahydro- and N.-methyl-tetrahydro-quinolines—

 and 

These substances are all useless, owing to their toxic action on the red blood-corpuscles.

Although the artificial quinoline derivatives have proved useless in medicine, a compound produced by Knorr,[1] with the intention of obtaining a substance resembling quinine, met with a great and surprising success. The compound in question was first considered by Knorr to possess a structure[2] similar to that which was then attributed to quinine. Later Knorr, however, showed that it was more closely related to pyrazole

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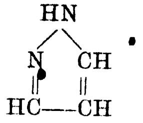
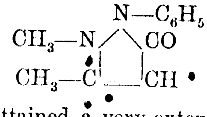
[1] *Annalen*, **238** (1887), 137.

[2] *Ber.*, **17** (1884), 2037.

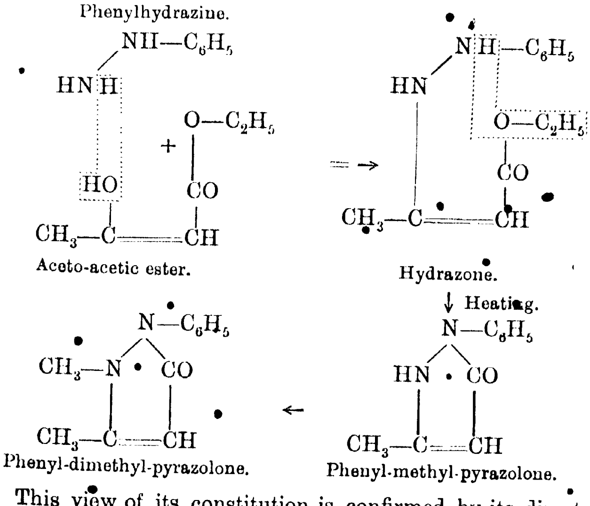


in structure, being in fact phenyl-dimethylpyrazolone—



This compound has attained a very extended use in medicine under the name of *antipyrine*.

It is obtained by the action of aceto-acetic ester on phenylhydrazine, whereby a hydrazone is formed, which on heating loses the elements of alcohol, with the formation of phenyl-methyl-pyrazolone. This is then heated with methyl iodide and methyl alcohol at 100-150° C., which transforms it into antipyrine.[1]



This view of its constitution is confirmed by its direct synthesis from $C_6H_5—NH—NH—CH_3$ and aceto-acetic ester.

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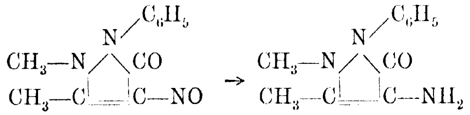
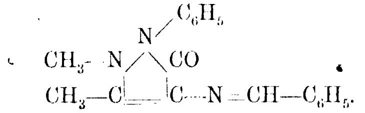
[1] D. R. P., 26,429, 33,536, 40,337, 42,726.

Its salt with acetylsalicylic acid (*cf.* p. 157) is known as *Acetopyrine.*

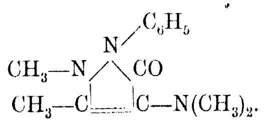
Antipyrine has a very strong antipyretic action, which is far greater than that of quinine, and it is free from injurious effect on the hæmoglobin, but it has no specific action against malaria. On the other hand, it has the very useful property of diminishing neuralgic pains (analgesic action), which has secured for it a great popularity. A large number of derivatives of antipyrine have been placed on the market, but most of these have no advantage over it, and many of them are very loose compounds of antipyrine and other substances, which act practically like mixtures. One derivative of antipyrine has, however, proved of great value, namely, 4-dimethyl-amino-antipyrine. This substance, which is called *Pyramidon* or *Amidopyrine*, is about three times as powerful in its action as antipyrine, and also has the advantage of being free from injurious effects on the heart (Kobert). It is prepared by treating an acid solution of antipyrine with sodium nitrite, whereby nitroso-antipyrine is formed. This on reduction gives amino-antipyrine—



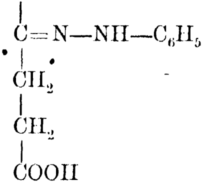
which is isolated in the form of its benzylidene derivative (*i.e.* condensation product with benzaldehyde)—



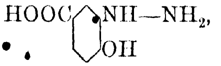
This is then decomposed with hydrochloric acid, and on methylation yields pyramidon—



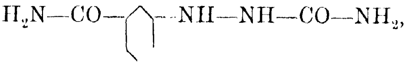
The success of antipyrine, and the mistaken idea that its action might belong to phenylhydrazine derivatives in general, led to the production of a large number of these, most of which are, however, without therapeutic value. The intense toxic action of phenylhydrazine is weakened by the entrance of acetyl groups, but the monoacetyl derivative (*hydracetin*), $C_6H_5{-}NH{-}NH\,.\,CO\,.\,CH_3$, and the diacetyl derivative, $C_6H_5NH{-}N(CO\,.\,CH_3)_2$, are both too toxic to be of any use. Other phenylhydrazine derivatives have been prepared, in which the carboxyl group enters the molecule, *e.g.* the hydrazone of lævulinic acid—



$$\begin{array}{l} CH_3 \\ | \\ C{=}N{-}NH{-}C_6H_5 \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ COOH \end{array}$$

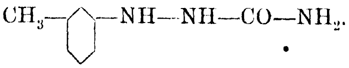
called *Antithermin*, but this, like *Orthin*,  and other derivatives of this type, is too toxic for use.

More success has attended a compound in which acid amide groups are introduced into the molecule, meta-benzaminsemicarbazide,



having been extensively used as an antipyretic under the name of *Cryogenin*.

Maretin is meta-tolylsemicarbazide,



Aniline Derivatives.

The antipyretics already described owe their origin to the endeavour to prepare substances similar to quinine. Those to be dealt with in the present section are based on the discovery of Cahn and Hepp,[1] that aniline and acetanilide have powerful antipyretic and anti-neuralgic properties, and the low price of aniline gave a still further stimulus to the endeavour to find a suitable derivative of it that could rival the more expensive quinine and antipyrine. Aniline and its salts have a strong antipyretic action, but they are readily absorbed, and owing to their action on the hæmoglobin, give rise to toxic symptoms.

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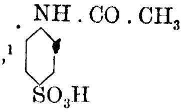
[1] *Zentralblatt f. klin. Med.*, 33 (1886); *Ber. klin. W.* (1887), 1 and 2.

By the entrance of an acetyl group, aniline is rendered more resistant and less toxic, so that *acetanilide*, $C_6H_5 . NH . CO . CH_3$, has been used in medicine under the name of "*antifebrin.*" It has marked antipyretic properties, and also acts as an analgesic. Though far less toxic than aniline, yet its physiological effect is due to the slow liberation of aniline, and after a time symptoms of aniline poisoning may become apparent. It is only used now on account of its cheapness—it is by far the cheapest of all antipyretics—and it forms the active ingredient of many of the secret remedies that are advertised for the cure of headaches, etc., and is also used to adulterate other more expensive drugs, such as phenacetin. Small quantities of acetanilide are oxidized in the body to para-aminophenol,[1] and the observation of this fact has led to the introduction of various derivatives of para-aminophenol as antipyretics. Before passing on to these, attention may be given to some other compounds which are more closely akin to acetanilide. In most of these cases the compounds that have been introduced could have no marked advantage over acetanilide, as they likewise depend on the liberation of free aniline for their physiological effect. For example, benzanilide and salicyl-anilide resemble acetanilide, but have to be given in bigger doses, as they are less readily split up in the intestine; while on the other hand, formanilide, owing to the ease with which it undergoes hydrolysis, is far more toxic than acetanilide. Toluidine derivatives also have not the slightest advantage over acetanilide, as all the three toluidines have, when once in the system, practically the same toxic action as aniline.

Attempts have been made to obtain more soluble derivatives of acetanilide by the introduction of acidic groups. As the sparing solubility of acetanilide does not have any injurious effect on its therapeutic action, these attempts must be regarded as quite unscientific, especially as the resulting compounds are, as was to be expected with acidic substances, quite inert and without the characteristic action of acetanilide. An example of this class is *Cosaprin*,[1] 

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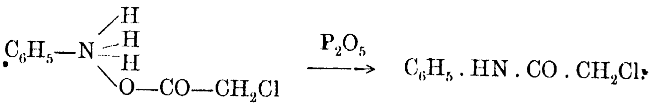
[1] Schmiedeberg, *A. e. P. P.*, 8 (1878), 1.

Substances containing a sulphonic acid group in the ω-position of the acetanilide molecule are said to be an exception to the rule that acidic substances are inert. These derivatives are said to be easily soluble and to have an antipyretic action, but they do not appear to have come into use, and it may therefore be that the original statements as to their antipyretic action were mistaken.

$C_6H_5 . NH . CO . CH_2 . SO_3Na$ is an example, and is prepared as follows: The aniline salt of chloracetic acid is treated with phosphorus pentoxide—



$$C_6H_5—N\begin{matrix}H\\H\\H\\O—CO—CH_2Cl\end{matrix} \xrightarrow{P_2O_5} C_6H_5 . HN . CO . CH_2Cl.$$

The product is then heated with an aqueous solution of sodium sulphite—

$$C_6H_5 . NH . CO . CH_2Cl + Na_2SO_3$$
$$= NaCl + C_6H_5 . NH . CO . CH_2 . SO_3Na,$$

the sodium salt of the acetanilide sulphonic acid separating on cooling.[2]

Methyl-acetanilide, $C_6H_5 . N(CH_3) . CO . CH_3$, *exalgin*, has toxic properties and is not much used in medicine.

An aniline derivative of a different type is phenyl-urethane, *Euphorin*, $C_6H_5 . NH . COOC_2H_5$. It is prepared by the action of aniline on chloro-formic ester—

$$C_6H_5 . NH_2 + Cl . COOC_2H_5 = C_6H_5 . NH . COOC_2H_5 + HCl.$$

It is far less toxic than aniline, and has marked analgesic properties, but is irregular in its antipyretic effect.

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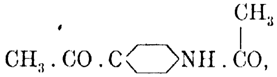
[1] D. R. P., 92,796.

[2] *Ibid.*, 79,714, 84,654.

DERIVATIVES OF PARA-AMINOPHENOL.

The use of para-aminophenol derivatives as antipyretics is due to the discovery that aniline and its simple derivatives are partially converted by the organism into para-aminophenol,[1] which is then eliminated as a sulphonic acid derivative or as a compound of glycuronic acid. Para-aminophenol is far less toxic than aniline, but it still has an action on the hæmoglobin sufficient to be harmful in moderate doses. The replacement of the hydrogen of the amino group by an acetyl group, with the formation of $HO\langle\quad\rangle NH\,.\,CO\,.\,CH_3$, yields a compound with a lower toxicity than para-aminophenol, and with anti-pyretic and anti-neuralgic properties, but still not quite satisfactory as a drug. The next step was the replacement of the hydroxylic hydrogen by radicles, and diacetyl-aminophenol,



$$CH_3\,.\,CO\,.\,C\langle\quad\rangle NH\,.\,\overset{\displaystyle CH_3}{\overset{|}{CO}},$$

was prepared, but it was found to be inferior in its action to para-ethoxy-acetanilide and para-methoxy-acetanilide, $C_2H_5O\langle\quad\rangle NH\,.\,CO\,.\,CH_3$, and $CH_3O\langle\quad\rangle NH\,.\,CO\,.\,CH_3$, which were named *phenacetin* and *methacetin* respectively.

The last-named compound was found to possess antipyretic and anti-neuralgic properties in the highest degree of all, but phenacetin, in which these properties are only slightly less well marked, has the advantage of having less toxic action on the blood. *Phenacetin*, which was the first drug of this class to be placed on the market, has retained the lead ever since, and is by far the most important compound of this class, and indeed, at the present time, is probably more used than any of the other antipyretic and analgesic substances.

The starting point for the synthesis of phenacetin is para-nitro-phenol. The sodium salt of this is treated with ethyl bromide, and the product reduced with tin and hydrochloric acid. The para-phenetidine thus formed is then acetylated by boiling with glacial acetic acid.[2]

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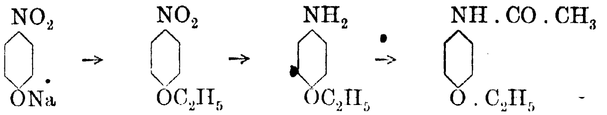
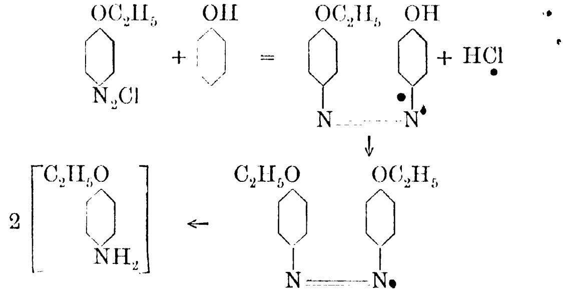
[1] Schmiedeberg, *loc. cit.*

[2] Paul, *Zeit. agwd. Chem.* (1896), 594; Hinsberg, *Annalen*, **305** (1899), 278; Hurst and Thorpe, *J. C. S.*, **107** (1915), 134.



Para-phenetidine. Acetyl para-phenetidine (phenacetin).

On the commercial scale, an ingenious variation of this process has been devised, whereby one molecule of para-nitrophenol is made to furnish a large number of molecules of phenacetin. This process is adopted on account of the fact that para-nitrophenol is rather difficult to obtain in the pure condition. In this process, the para-nitrophenol is converted into para-phenetidine by the method already described, and the phenetidine is then diazotized and coupled with phenol in the presence of sodium carbonate. This is then ethylated, and the product thus obtained is then reduced, whereby two molecules of phenetidine are obtained. These can then be converted into phenacetin by acetylation, or can be made to yield a double quantity of phenetidine by repeating the above-described process[1] of diazotization and coupling with phenol.



Phenacetin is also obtained by the ethylation of p-acetylamino phenol.[2]

Phenacetin is only slightly toxic, but when given in very large doses, some methæmoglobin is found in the blood. Its antipyretic action is due to increased heat-loss from the surface of the body, but this drug is used chiefly for its analgesic action, in the treatment of headache, neuralgia, etc.

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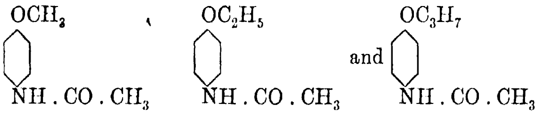
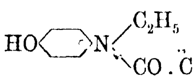
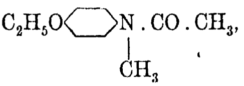
[1] D. R. P., 48,543.

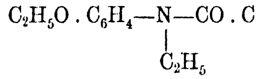
[2] *Ibid.*, 85,988 ; Hinsberg, *loc. cit.*

Several other derivatives of the phenacetin group have been prepared, but none of them have any novel therapeutic action, as in all of them this depends on the liberation of para-amino-phenol or para-phenetidine in the body. Indeed, it has been shown by Treupel and Hinsberg,[1] that the antipyretic action of aniline and para-amino-phenol derivatives is, within certain limits, proportional to the amount of aniline, para-amino-phenol or phenetidine, formed in the organism. This statement is based on the fact that, in those cases where an antipyretic action is found, the urine shows the indophenol reaction, and that the intensity of the reaction is roughly proportional to the strength of the antipyretic effect. This reaction is carried out as follows: The urine is acidified with two drops of hydrochloric acid, and two drops of a one-per-cent. solution of sodium nitrite added, whereby the phenetidine (or other primary amine) is diazotized. On adding an alkaline solution of β naphthol, a red coloration is produced, which becomes violet on acidifying with hydrochloric acid. This reaction is given by—



which resemble phenacetin in their physiological action, but not by 

, which has no antipyretic action, and no action on the blood. If, however, the hydrogen of the amino group is substituted in phenacetin itself, physiologically active substances are obtained. For example, the methyl derivative, 

, has greater narcotic and anti-neuralgic properties, but less antipyretic action than phenacetin, while in the ethyl derivative, 
$C_2H_5O\,.\,C_6H_4\underset{\overset{|}{C_2H_5}}{—N—}CO\,.\,CH_3$, there is an increase in the narcotic power, accompanied by a decrease in the toxic properties, the antipyretic action being retained with

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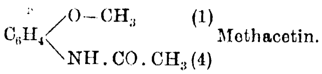
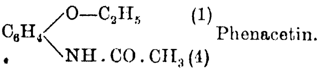
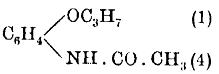
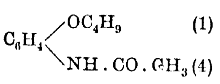
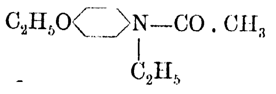
[1] *A. e. P. P.*, 33 (1894), 216.

slightly diminished intensity. In the higher members of the series, such as the propyl and butyl derivatives, the narcotic and anti-neuralgic properties rapidly diminish with the increase in the molecular weight. In this series the maximum antipyretic and anti-neuralgic effect is shown by the methyl and ethyl derivatives, and the minimum toxicity by the ethyl compound. This corresponds to the effect of substituting the *hydroxylic* hydrogen of amino-phenol by alkyl groups, which is illustrated by the following table, showing the alteration of the physiological effect produced by the entrance of alkyl groups in the hydroxyl of acetyl-amino-phenol :—

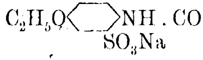
Formula and Name of Substance.	Physiological Effect Compared to that of p.-acetyl-amino-phenol.
 $C_6H_4\left<\begin{matrix}O-CH_3 & (1)\\ NH.CO.CH_3 & (4)\end{matrix}\right.$ Methacetin.	Anti-pyretic and anti-neuralgic effect strengthened. Less blood toxicity.
 $C_6H_4\left<\begin{matrix}O-C_2H_5 & (1)\\ NH.CO.CH_3 & (4)\end{matrix}\right.$ Phenacetin.	Anti-pyretic action maintained, analgesic action strengthened. Much less blood toxicity.
 $C_6H_4\left<\begin{matrix}OC_3H_7 & (1)\\ NH.CO.CH_3 & (4)\end{matrix}\right.$	Anti-pyretic action slightly weakened. Blood toxicity diminished, but toxicity greater than with methacetin and phenacetin.
 $C_6H_4\left<\begin{matrix}OC_4H_9 & (1)\\ NH.CO.CH_3 & (4)\end{matrix}\right.$	Anti-pyretic action weakened.

This table shows the superiority of phenacetin over the other members of the homologous series. The only substance as yet mentioned which appears to have any possible advantage over phenacetin is its substituted ethyl derivative—



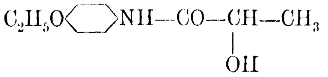
$$C_2H_5O\langle\;\rangle N(C_2H_5)-CO.CH_3$$

In this case, its possible slight advantages are probably outweighed by its increased cost.

Owing to the slight solubility of phenacetin, many attempts have been made to prepare more soluble derivatives, which should nevertheless be sufficiently stable to resist the action of the dilute hydrochloric acid of the gastric contents, and so prevent the liberation of poisonous phenetidine salts. As the slight solubility of phenacetin does not appear to interfere with its physiological effect, these efforts are not of great practical value. The introduction of sulphonic acid or carboxyl groups in order to obtain increased solubility, was not likely to meet with much success, as generally the presence of acid groups tends to destroy the physiological activity of a compound. For example, both the sulphonic and the carboxylic acid of phenacetin are almost inert, but the sodium salt of the former has been introduced under the name of *Phesin*,  $C_2H_5O\langle\quad\rangle NH . CO . CH_3$ (with SO_3Na on the ring), and is said to have slight temporary antipyretic properties.

Similar compounds to phenacetin have been prepared in which the hydrogen of the amino group is replaced by acid radicles other than acetyl. Para-propionyl-phenetidine (*Triphenin*) is similar to phenacetin, but less soluble and hence less physiologically active.

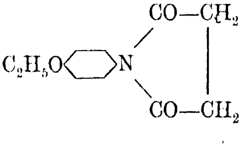
Lactyl-phenetidine (*Lactophenin*)—



$$C_2H_5O\langle\quad\rangle NH{-}CO{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3$$

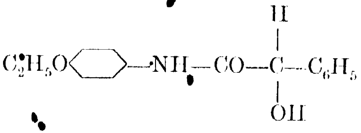
is more soluble than phenacetin, and has less anti-pyretic action, but has well-marked anti-neuralgic and narcotic properties. It is more liable to liberate toxic phenetidine hydrochloride.

Para-ethoxy-phenyl-succinimide (*Pyrantin*)—



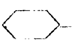
and diacetyl-phenetidine, $C_2H_5O\langle\quad\rangle N(COCH_3)_2$, have been prepared, but have no value.

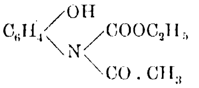
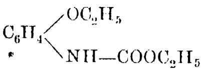
Salicyl-phenetidine is stable, insoluble, and practically inert, as would be expected, and amygdophenine—



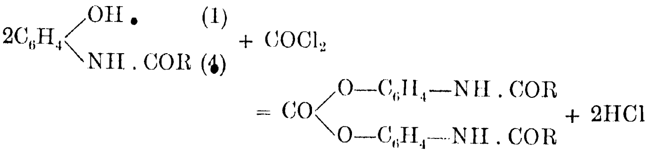
$$C_2H_5O\langle\quad\rangle—NH—CO—\overset{\overset{|}{H}}{\underset{\underset{OH}{|}}{C}}—C_6H_5$$

is also rather insoluble and inert. It is the mandelic acid derivative of phenetidine.

It has been noticed that phenyl-urethane, *Euphorin*, —NH.CO.OC$_2$H$_5$, is partially oxidized by the organism into para-hydroxy-phenol-urethane, and some of its derivatives have been prepared for pharmaceutical purposes.

 $C_6H_4\left<\begin{matrix}OH\\ N\left<\begin{matrix}COOC_2H_5\\ CO.CH_3\end{matrix}\right.\end{matrix}\right.$	Acetyl p.-hydroxyphenyl-urethane (neurodin).	Very insoluble in cold water. Rapid but uncertain anti-pyretic action.
 $C_6H_4\left<\begin{matrix}OC_2H_5\\ NH—COOC_2H_5\end{matrix}\right.$	Para-ethoxy-phenyl-urethane.	More certain anti-pyretic action.

The acetyl derivative of the last-named above has been introduced under the name "*Thermodin.*" It has a gradual anti-pyretic action, is not toxic, and has no depressant action on the heart or respiration. It is insoluble except in acid media. Various derivatives of this type have been prepared by Merck,[1] by passing carbonyl chloride into a solution of para-oxyphenyl-urethane, or acid derivatives of para-phenetidine in presence of alkalies—



$$2C_6H_4\left<\begin{matrix}OH & (1)\\ NH.COR & (4)\end{matrix}\right. + COCl_2 = CO\left<\begin{matrix}O—C_6H_4—NH.COR\\ O—C_6H_4—NH.COR\end{matrix}\right. + 2HCl$$

where R = CH_3, C_2H_5, C_6H_5, OC_2H_5, or OC_3H_7.

If the reaction is carried out in alcoholic solution in presence of sodium ethoxide, mixed carbonates are formed—

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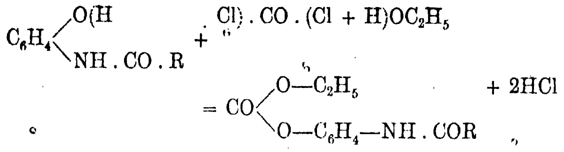
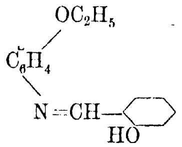
[1] D. R. P., 69,328, 85,803.

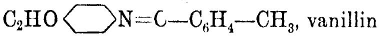


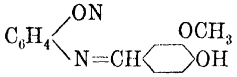
$$C_6H_4\left\langle\begin{matrix}O(H\\NH.CO.R\end{matrix}\right. + \left.Cl\right).CO.(Cl + H)OC_2H_5 = CO\left\langle\begin{matrix}O—C_2H_5\\O—C_6H_4—NH.COR\end{matrix}\right. + 2HCl$$

By varying the alcohol, methyl or propyl groups can replace the ethyl group.

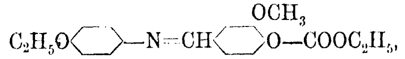
Among other derivatives of phenetidine which have been prepared are certain condensation products with aldehydes. Mention may be made of *Malakin*—



prepared by condensing phenetidine with salicylic aldehyde,[1] *Malarin*,[2] the citrate of methyl-benzylidene-phenetidine, , vanillin-phenetidine[3]—

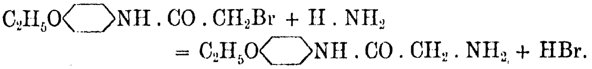


(said to be a good styptic) and the para-phenetidine derivative of vanillin ethyl carbonate[4]—



which has been named *Eupyrin*. None of these are, however, of any particular value.

A soluble derivative of phenacetin has been prepared by Schmidt and Majert, by the action of ammonia on bromacetyl-phenetidine (bromo-phenacetin)—



The amino-phenacetin thus formed is named *Phenocoll*. Its hydrochloride is readily soluble in water, and has a similar action to phenacetin, but the action appears and disappears more rapidly. It is said to have a greater analgesic action, and also to have antiseptic properties, and to be a good substitute for salicylic acid as an anti-pyretic in rheumatic fever. Its only insoluble salt is the salicylate, *Salocoll.*

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[1] D. R. P., 79,814, 79,857.

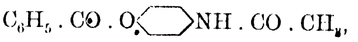
[2] *Ibid.*, 87,897, 98,840.

[3] *Ibid.*, 96,342.

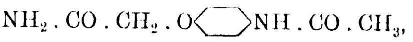
[4] *Ibid.*, 101,684.

So far, mention has only been made of phenetidine derivatives in which the hydrogen of the hydroxyl group has been replaced by simple alkyl groups, but several derivatives have been prepared where this hydrogen has been replaced by more complex groups.

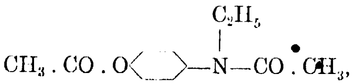
For example, acetylamino-phenyl benzoate—



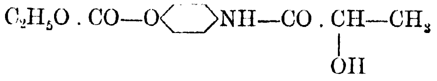
acetylamino-phenol acetamide—



acetyl-ethylamino-phenol acetate—



and lactyl-amino-phenyl ethyl carbonate—



have been prepared and described, but do not appear to have had any practical application.

CHAPTER VI.

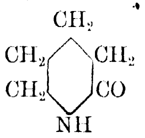
ALKALOIDS.

A DISCUSSION of the chemistry of the alkaloids would be out of place in this work, and the reader who desires further information on this head is referred to special works dealing with the subject, such as Pictet's "Vegetable Alkaloids." Nevertheless, it is of interest to mention some of the recent work that has been carried out in this field, a good deal of which has not yet found its way into the text-books; much of this is to be found in the section dealing with the isoquinoline alkaloids.

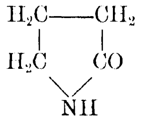
No precise and satisfactory definition of the term "alkaloid" can be given, and it has generally been used to denote nitrogenous basic substances of a cyclic structure found in plants, but it seems advisable to restrict its use to substances possessing a more or less marked physiological action. The alkaloids possess a special interest for the study of the relation between physiological action and chemical constitution, owing to the fact that many of them, even in small doses, produce very marked and definite physiological effects, and that a slight alteration in the chemical structure of the molecule often produces a decided change in this effect.

Mention has previously been made of the fact that the reduction of a nitrogenous ring generally produces a marked increase in the toxicity and strength of the action of the drug, and sometimes completely alters its character. For example, pyridine has no marked toxic action and lowers blood-pressure, but piperidine is very toxic and raises blood-pressure. β-naphthylamine is not very poisonous, and contracts the pupil of the eye, but tetrahydro-β-naphthylamine is more poisonous and dilates the pupil. Many other examples of this type will be encountered from time to time. In all cases it is probably connected with the fact that reduction causes the substance more nearly to approach the aliphatic bodies in its properties, while in the case of pyridine and quinoline rings, it is connected with the change from tertiary nitrogen to the more reactive secondary form.

Although the substances containing reduced rings are more active physiologically than those containing pyridine or quinoline rings, yet the activity is often apparently dependent upon the cyclic structure, as the open chain compounds are in general much less active than the corresponding alicyclic ones, and nearly all the active alkaloids are possessed of a cyclic structure. For example, δ-amino-valerianic acid and γ-amino-butyric acid are without any particular physiological action, but their anhydrides, the cyclic bases piperidone—



and α-pyrrolidone—



have a powerful action.[1] In the same way pentamethylene-diamine, $NH_2[CH_2]_5NH_2$, is not toxic, while piperidine is.

The size and position of the side chains attached to the ring have an important effect, and in some cases relationships have been traced between these factors and the physiological action. Thus, most of the alkaloids are derivatives either of pyridine itself, or of quinoline or isoquinoline, both of which latter contain a conjugated pyridine nucleus. Pyridine has only a slight physiological action, but more active bodies are generally obtained by reduction or by the entrance of aliphatic side chains. The introduction of the latter is accompanied by the appearance of intoxicating action, which increases with the length and the number of the side chains.[2] The toxic action of piperidine itself is not very strong, but it is increased in α-methyl piperidine (pipecoline), and still more in α-ethyl piperidine and α-propyl piperidine (coniine). The toxicity of these substances

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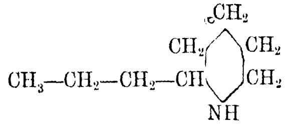
[1] Schotten, *Ber.*, 21 (1888), 2243; Gabriel, *Ber.*, 23 (1890), 1772, 3335.

[2] Kendrick and Dewar, *Proc. Roy. Soc.*, 22 (1874), 432.



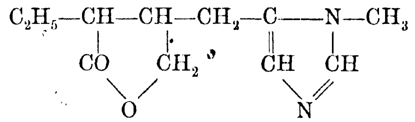
is in the ratio of 1 : 2 : 4 : 8.

In a previous chapter reference has been made to the remarkable discovery of Crum Brown and Fraser on the effect of transforming a tertiary base into a quaternary ammonium compound. In the case of almost every alkaloid which is a tertiary base, the original action disappears and is replaced by a curare-like action. The quaternary methyl and ethyl derivatives of atropine are partially exceptional; they resemble atropine itself in their action on the sympathetic nervous system, but differ from it in their action on the central nervous system and in having a curare-like action. Thus, atropine-methyl-nitrate retains the mydriatic action of atropine, while the action of atropine on the brain is lacking in this substance and also in the alkyl bromides of atropine and the allied alkaloids, hyoscyamine, homatropine, and scopolamine.

The effect of the presence of hydroxyl groups, carboxyl groups, unsaturated linkages, etc., has already been dealt with in a previous chapter, and the special importance of the esterification of hydroxyl groups by acid radicles in alkaloids will be discussed in connection with cocaine, heroin, etc.

Of the alkaloids which are used in medicine, caffeine, theobromine, and the other purine derivatives are often considered separately, on account of their close relationship to various non-alkaloidal substances, such as uric acid, xanthine, etc. These alkaloids and their derivatives will therefore be considered in another chapter. The morphine group, the isoquinoline derivatives, and the derivatives of tropine will be considered in the following sections, and there remain quinine, pilocarpine, and strychnine as being important from the medicinal point of view. Nicotine and many other alkaloids are also of great interest, but they are not much used in medicine, and comparatively little work has been done on them during recent years.

It has been shown by the work of Jowett[1] and of Pinner[2] hat pilocarpine probably has the constitution represented by he formula—



nd that isopilocarpine is probably a stereo-isomeride. This lkaloid has not yet been synthesized, nor have synthetic subtances of similar constitution and physiological action been ntroduced into medicine, and therefore it need not be conidered at length. Pilocarpine illustrates the difficulty often ncountered in correlating chemical constitution and physioogical action. Pharmacologically, it is very similar in many espects to muscarine (hydroxycholine, $(HO)_2C_2H_3N(CH_3)_3OH$), o which it bears no particular chemical relationship. On the ther hand, it may be pointed out that pilocarpine resembles icotine in some of its physiological effects, and that both subtances contain a five-membered ring containing nitrogen. It s true that nicotine also contains a six-membered nitrogen ing, but its physiological action is probably due more to the ive-membered pyrrolidine ring. (*Cf.* quinine.)

Our knowledge of the constitution of strychnine is not in proortion to its importance in medicine; in fact, until recently no onstitutional formula had been proposed for it, but lately erkin and Robinson[3] have tentatively suggested that the tructure of this substance may be represented by the forula on next page.

With regard to quinine, our knowledge is more satisfactory, nd although its synthesis has not yet been accomplished, a reat deal of synthetic work has been carried out in connection ith it, and therefore a more extended account of this alkaloid ill not be out of place.

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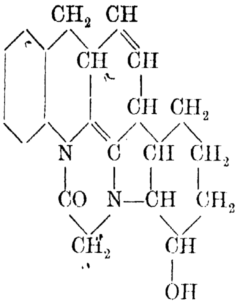
[1] *J. C. S.*, **77** (1900), 473, 851; **79** (1901), 580, 1331; **83** (1903), 438, 34; *Proc. Chem. Soc.*, **21**, 172.

[2] *Ber.*, **33** (1900), 1424, 2357; **34** (1901), 727; **35** (1902), 192, 2441.

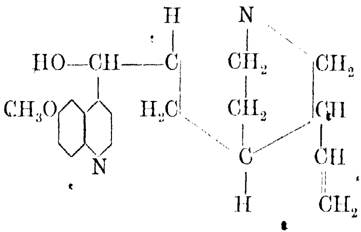
[3] *J. C. S.*, **97** (1910), 305.



Strychnine.

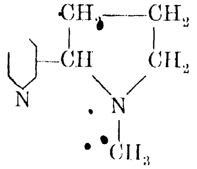
The therapeutic value of quinine arises chiefly from the fact that it appears to have a specific action in malaria, probably being far more poisonous to the protozoal parasites than to the cells of the host. It has also been widely used as a febrifuge, but this is referred to in the chapter on anti-pyretics, and at present it is proposed to consider its properties from the same point of view as those of the other alkaloids.

Quinine was isolated, together with cinchonine, by Pelletier and Caventou in 1820, and as a result of the labours of many chemists, of whom Skraup, Königs, von Miller, and Rhode may be specially mentioned, the following formula has been generally accepted to represent its constitution—

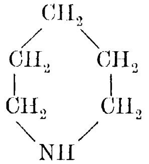


that of cinchonine only differing from it by the absence of the methoxy group, (—OCH_3), and that of cupreine only in having this group replaced by an hydroxyl group, (OH).

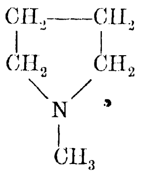
The earlier attempts to prepare substances which should resemble quinine in their properties were based on the assumption that the quinoline nucleus was the active portion of the molecule, but Fraenkel[1] brings forward many facts in support of the view that it is the piperidine ring, the so-called "loiponic acid portion" of the molecule, which is the true "pharmacophore." Thus, it is pointed out that in nicotine—



the contraction of the blood-vessels is almost certainly due to the pyrrolidine and not to the pyridine ring, seeing that this action is not shown by pyridine at all, but *is* produced by piperidine—



pyrrolidine, and N.-methyl pyrrolidine—



the last named closely resembling nicotine in this respect.[2] In the same way it is considered that the action of quinine is due to the reduced piperidine ring, which is rendered still more active by the presence of the unsaturated group, $—CH{=}CH_2$. The weak and uncertain action of cinchonine, compared with that of quinine, is probably owing to the absence of the para-methoxy group leaving the molecule without an "anchoring" group. Owing to this, the hydrogen atom of the quinolin nucleus probably has to become oxidized to OH with the formation of cupreine before it can exert the characteristic quinine action.

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[1] "Arzneimittel-synthese," p. 231 (1906).

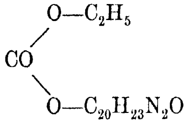
[2] Tunnicliffe and Rosenheim, *Centralbl. für Physiol.*, 16 (1902), 93.

Many attempts have been made to prepare derivatives of quinine which should be free from some of its unpleasant by-effects, especially its bitter taste, and also to prepare derivatives which should be more soluble than the generally used sulphate, and so be suitable for hypodermic injection. Of the latter class, mention should be made of the double chloride and sulphate of quinine, which is very soluble in water, and of the double chloride of quinine and caffeine, which is readily soluble and suitable for hypodermic injection. Cinchonine is less bitter than quinine, but its action is weak and untrustworthy, and so it is not a suitable substitute. If quinine is converted into insoluble derivatives its taste is diminished, and a favourite derivative of this class is the tennate, which is practically tasteless, but suffers from the drawback that it is only slowly split up in the intestine into its components, and is therefore lacking in promptitude and certainty.

Other derivatives have been prepared by esterification of the hydroxyl group, the most important of these being the esters of carbonic acid.[1] The diquinine ester of carbonic acid

$$C_{20}H_{23}N_2O—O—CO—O—C_{20}H_{23}N_2O,$$

is known as *Aristoquinine*, and is comparatively tasteless and fairly insoluble.[2] *Euquinine* is the ethyl carbonate of quinine—



$$CO\begin{cases} O—C_2H_5 \\ O—C_{20}H_{23}N_2O \end{cases}$$

and is prepared by the action of ethyl chloro-formate, $Cl.COOC_2H_5$, on quinine.[3] It is practically tasteless, and does not have a bitter after-taste. The hydrochloride, on the other hand, is not as good as the free base, and has no advantage over quinine itself.

Phenetidine quinine carbonic ester—

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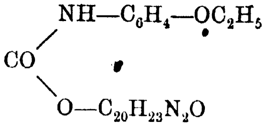
[1] D. R. P., 90,848, 93,698, 118,122.

[2] *Ibid.*, 134,307, 134,308.

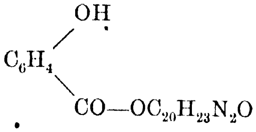
[3] *Ibid.*, 91,370.



$$CO\begin{cases} NH-C_6H_4-OC_2H_5 \\ O-C_{20}H_{23}N_2O \end{cases}$$

is known as *Quinaphenin.*

Saloquinine is the salicylic acid ester of quinine—



$$C_6H_4\begin{cases} OH \\ CO-OC_{20}H_{23}N_2O \end{cases}$$

and is tasteless.

Quinaphthol is quinine β-naphthol-sulphonate, and *Quinaform* is quinine formate.

In all these compounds, absence of taste is conditioned only by insolubility, their more soluble derivatives having the characteristic bitter taste of quinine. The more soluble hydrochloride of euquinine is an instance of this.

CHAPTER VII.

ATROPINE AND THE TROPEINES—COCAINE AND THE LOCAL ANÆSTHETICS.

ATROPINE and cocaine are closely related, not only in their chemical constitution, but also in their physiological action, both of them causing dilatation of the pupil (mydriatic action).

Atropine and the Tropeines.—Atropine was discovered in 1831 in the roots of the belladonna plant, and is a strongly poisonous alkaloid. Its chief use in medicine depends upon its action in dilating the pupil and paralysing the accommodation of the eye, and it is also used to check the inhibition of the heart arising from administration of chloroform and the depressent action of morphine on the respiratory centre.

Atropine is an ester, and on hydrolysis yields a basic substance, *tropine*, an optically inactive tropic acid.[1] It has been shown that the alkaloid hyoscyamine, which is also obtained from belladonna and is lævo-rotatory, is the ester of tropine with lævo tropic acid,[2] and therefore atropine appears to be racemic hyoscyamine. This view of the nature of atropine has been confirmed by Ladenburg,[3] and dextro-hyoscyamine has also been prepared by the union of tropine with dextro tropic acid.[4]

The pharmacology of these three stereo-isomerides, *d.*-hyoscyamine, *l.*-hyoscyamine, and the racemic form, atropine, has been investigated by Cushny,[5] using the frog as the subject of the experiments. It was found that all three were alike in certain respects, but that with regard to some aspects of their action, dextro-hyoscyamine was the strongest and the lævo variety the weakest, while with other effects of the drug exactly the reverse was the case. In all cases the action of atropine was intermediate between that of the two optically active forms, and this fact is explained by Cushny by the assumption that atropine is probably decomposed in solution into its two active components.

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[1] Kraut, *Annalen*, **128** (1863), 273; **133** (1865), 87; **148** (1868), 236. Lossen, *Annalen*, **131** (1864), 43; **138**, 230.

[2] Gadamer, *A. Pharm.*, **239** (1901), 294.

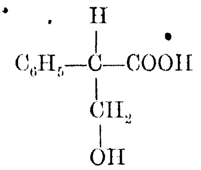
[3] Ladenburg, *Ber.*, **21** (1888), 3065.

[4] Amenomiya, *A. Pharm.*, **240** (1902), 498.

[5] Cushny, *Journ. of Physiol.*, **30** (1903), 176.

As atropine is the ester of tropine with racemic tropic acid, it is obvious that a knowledge of the constitution of these two substances is necessary in order to know that of atropine.

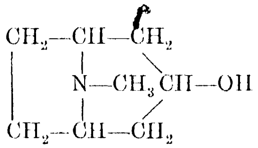
Tropic acid is a relatively simple substance, being indeed a homologue of mandelic acid, and having the constitution—



$$\begin{array}{rcl} & H & \\ & | & \\ C_6H_5\text{—} & C & \text{—}COOH \\ & | & \\ & CH_2 & \\ & | & \\ & OH & \end{array}$$

This view of its structure has been confirmed by a synthesis of the acid.[1]

The question of the constitution of tropine is one which has presented far greater difficulties, but thanks to the researches of Ladenburg, Merling, Willstätter, and others, our knowledge of the constitution of this substance is as complete as that of any alkaloid, and there is no doubt that it is represented by the formula—



and this has been confirmed by Willstätter's brilliant synthesis.[2]

The constitution of this substance is of great importance, as not only does it show that atropine and hyoscyamine are represented by the formula—

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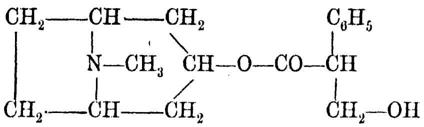
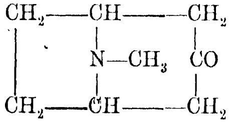
[1] Ladenburg and Rügheimer, *Ber.*, 13 (1880), 376; *Annalen*, 217 (1880), 74.

[2] Willstätter and Iglauer, *Ber.*, 33 (1900), 1170; Willstätter, *Ber.*, 34 (1901), 129, 3163; *Ibid.*, *Annalen*, 317 (1901), 307.

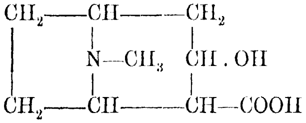


but it also explains the constitution of many other alkaloids which are derivatives of it.

For example, when tropine is heated with sodium and amyl alcohol, it is converted into a substance which is stereo-isomeric with it,[1] and which is identical with the substance pseudo-tropine, obtained by the hydrolysis of the coca alkaloid, tropa-cocaine (benzoyl-pseudo-tropine).[2] Both tropine and pseudo-tropine yield the same substance on oxidation, namely tropinone, and this on reduction yields pseudo-tropine and not tropine itself.



Tropinone.



Ecgonine.

It has been shown that cocaine is a derivative of ecgonine, which is in turn a carboxylic acid of tropine, and hence our knowledge of the constitution of this important alkaloid is also dependent on that of tropine.

Having accomplished the synthesis of atropine by combining tropine with tropic acid, Ladenburg prepared other esters of tropine with various organic acids, to which he gave the name *tropeines*.[3] Other tropeines have been prepared by Merck, Ladenburg, and others, and these substances are of great interest, as their mydriatic action can be easily compared, and hence they afford a convenient series of compounds for studying the relation between chemical constitution and physiological action. It was found that the tropeines derived from benzoic and cinnamic acids were without mydriatic action, as also was that from lactic acid, but those derived from mandelic and atrolactinic acid possess mydriatic properties.

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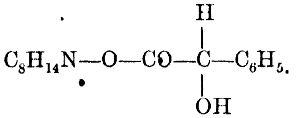
[1] Tropine is optically inactive, and so also is pseudo-tropine; the isomerism is dependent on *molecular* asymmetry (cis-trans isomerism).—Barrowcliff and Tutin, *J. C. S.*, **95** (1909), 1966.

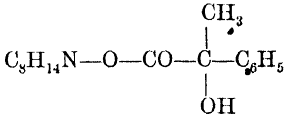
[2] For further details of these processes, see next section on Cocaine and Local Anæsthetics.

[3] *Ber.*, **13** (1880), 106, 1080, 1137, 1549; **15** (1882), 1025; **22** (1889), 2590; *Annalen*, **217** (1880), 74.



$$C_8H_{14}N{-}O{-}CO{-}\overset{\displaystyle H}{\underset{\displaystyle OH}{C}}{-}C_6H_5.$$

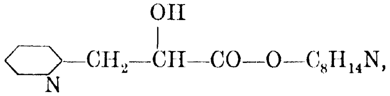
Mandelic.



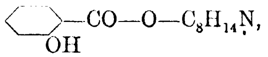
$$C_8H_{14}N{-}O{-}CO{-}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}{-}C_6H_5$$

Atrolactinic.

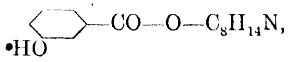
It will be noticed that the substances mentioned as having a mydriatic action, all contain both a benzene ring and an aliphatic hydroxyl group in the side chain containing the —O—CO group, and a statement has found its way into a good deal of the literature of the subject under the name of "Ladenburg's Rule," that only those tropeines which possess these characteristics have a mydriatic action. The so-called rule was never enunciated by Ladenburg, and it has been shown by Jowett and Pyman to be incorrect.[1] For example, they found that the following three tropeines all have a mydriatic action: α-hydroxy-β-2 pyridyl-propionyl tropeine—



ortho-hydroxy-benzoyl tropeine (salicyl tropeine),



meta-hydroxy-benzoyl tropeine,



although the first contains no benzene nucleus, and the second and third no aliphatic hydroxyl group.

The tropeine derived from mandelic acid is known as *homatropine*,[2] as it is the lower homologue of atropine—

$$C_8H_{14}N{-}O{-}CO{-}CH(OH){-}C_6H_5$$

Homatropine.

$$C_8H_{14}N{-}O{-}CO{-}CH(CH_2\,.\,OH){-}C_6H_5$$

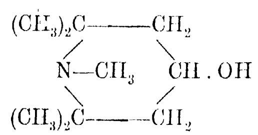
Atropine.

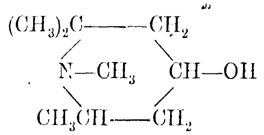
[1] *J. C. S.*, **95** (1909), 1090.

[2] D. R. P., 95,853.

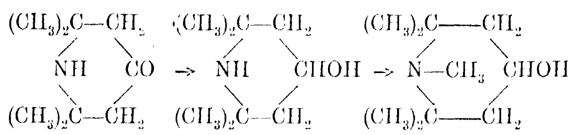
It is widely used in ophthalmic practice as a substitute for atropine, as its mydriatic action is nearly as great, and it has the advantages of being less toxic; moreover, its mydriatic action develops and passes off more rapidly.

Other esters have been prepared which resemble the tropeines to some extent in their chemical structure, and also have a mydriatic action, namely, the esters derived from triacetone-methyl-alkamine, and its lower homologue vinyl diacetone alkamine.





The structure of these substances is closely related to that of tropine. The former is prepared by reduction and methylation of triacetonamine—[1]



a process carried out by Fischer,[2] who also showed the relation between this substance and tropine. Its ester with mandelic acid resembles homatropine and atropine in having mydriatic action.

The preparation of N.-methyl-vinyl-diacetone-alkamine and some of its derivatives will be described later in connection with substitutes for cocaine, but for the present attention need only be drawn to the fact that various derivatives of the tropeine type have been prepared from it,[3] some of which have a mydriatic action. This substance, methyl-vinyl diacetonamine, exists in two forms, one, *a*, melting at 137-138° C., and the other, *β*, melting at 160-161° C. The existence of two asymmetric carbon atoms ([illegible])—

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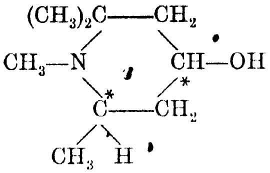
[1] Heinz, *Annalen*, **189**, 214; **191**, 124; **198**, 69.

[2] Fischer, *Ber.*, **16** (1883), 1604, 2236; **17** (1884), 1797.

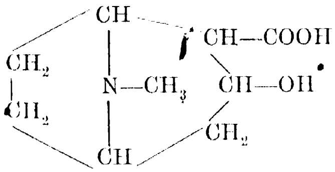
[3] Harries, *Annalen*, **294** (1896), 336; **296** (1897), 328.



in the molecule explains the existence of these two forms as stereo-isomerides, and it is interesting to note that it is only the mandelic ester derived from the β-derivative which possesses mydriatic properties.[1] This furnishes an interesting example of the difference in physiological action of stereo-isomerides.

Cocaine and the Local Anæsthetics.—The alkaloid cocaine was discovered in coca leaves in 1860.[2] It had long been known that the South American Indians were in the habit of chewing these leaves as a stimulant to enable them to stand great exertion without fatigue. The first use of cocaine in this country was for a similar purpose, but its great importance among alkaloids at the present time is due chiefly to Koller's important discovery that cocaine is a powerful and rapid local anæsthetic.

By hydrolysis with alkalies, cocaine yields ecgonine, benzoic acid, and methyl alcohol. Ecgonine was shown by Willstätter to be a carboxylic acid of tropine—



and by treatment with benzoyl chloride to yield benzoyl-ecgonine, in which the hydroxyl group is converted into O—CO . C_6H_5; this on conversion into its methyl ester yields cocaine, which therefore has the formula—

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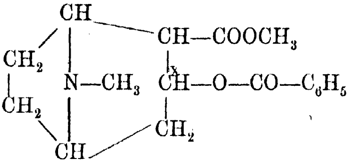
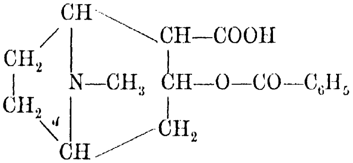
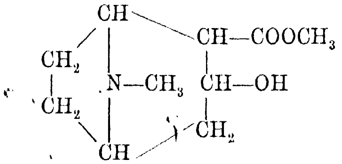
[1] Harries, *Ber.*, **29** (1896), 2730.
[2] Neumann, *Annalen*, **140** (1860), 213.



It is found that the free carboxylic acid, benzoyl-ecgonine itself, has no local anæsthetic action, but that any of its alkyl esters, such as ethyl, propyl, etc., resemble its methyl ester, cocaine, in having this action.[1] This applies only to the aliphatic esters, as the aromatic do not appear to have been prepared as yet. The effect of esterification is probably accounted for by an alteration of the anchoring group.



Benzoyl ecgonine (type of first series of esters).



Ecgonine methyl ester (type of second series of esters).

Ecgonine can be esterified in the usual way, leaving the hydroxyl group intact, and in this manner another series of esters can be obtained. Ecgonine methyl ester has no local anæsthetic action, but can be converted into cocaine by benzoylating the hydroxyl group. In this case, however, the nature of the group used to esterify the *hydroxyl* is important, for if the benzoyl group is replaced by others, the anæsthetic property is lost or greatly diminished.

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[1] Merck, *Ber.*, **18** (1885), 2954; **21** (1888), 48; Novy, *Amer. Chem. Journ.*, **10** (1888), 147.

Thus truxilline[1] (isatropyl-cocaine) has no anæsthetic action, but is a strong cardiac poison, and Ehrlich[2] found that, of several different cocaine derivatives, such as isatropyl-cocaine, valeryl-cocaine hydriodide, and phenylacetyl-cocaine hydriodide, the last named was the only one which had anæsthetic properties, but to a less degree than cocaine. All of these have a characteristic toxic effect on the liver, and differ from cocaine only in having the benzoyl group replaced by the one named.

Cocoa leaves, which are the only commercial source of cocaine, contain various other alkaloids, most of which are, however, devoid of the useful physiological properties of cocaine. These other alkaloids are amorphous substances which yield ecgonine on hydrolysis, and therefore, owing to the high price of cocaine, various methods have been devised to utilize them in improving the yield of cocaine obtainable from the leaves. According to one method,[3] the alcoholic solution of the amorphous bases is boiled with hydrochloric acid, filtered from the precipitated organic acids, and practically pure ecgonine hydrochloride obtained by evaporation of the filtrate. By means of benzoyl chloride or benzoic anhydride, this is converted into benzoyl-ecgonine, which is then esterified with methyl alcohol giving cocaine. Various modifications of this method have also been devised.[4]

Cocaine has several disadvantages when used for hypodermic injection, one of the most serious being that its solutions do not keep well, but become mouldy and decompose on boiling, so that they cannot be readily sterilized. For this reason, and also on account of the high price of cocaine, various attempts have been made to prepare analogous compounds which it was hoped would resemble cocaine in its useful physiological effects. As cocaine is a derivative of ecgonine, which is closely related to tropine, and as atropine, one of the esters of tropine, has a slight anæsthetic action, various attempts have been made to prepare substances from tropine which should have an action resembling that of cocaine. Several synthetic tropeines have been prepared, and have already been discussed, but none of these are of value as substitutes for cocaine. Strangely enough, however, a natural tropeine was discovered in Java coca leaves,[1] which is a stronger local anæsthetic than cocaine.[2] This substance, which is called tropacocaine, also has the advantage over cocaine in being less toxic and more resistant to microorganisms, and hence its solutions can be preserved for some length of time. It is the benzoyl ester of pseudo-tropine,[3] which only differs from ordinary tropine in its space configuration. It differs from cocaine and atropine in having no mydriatic action, and in this respect it resembles the other pseudo-tropeines, such as those of mandelic acid and tropic acid.

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[1] Liebermann, *Ber.*, **21** (1888), 2347.

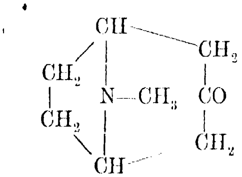
[2] Ehrlich, *Deutsche med. W.*, **32** (1891), 717.

[3] Liebermann and Giesel, D. R. P., 47,602.

[4] Einhorn and Klein, *Ber.*, **21**, 3335; D. R. P., 47,713. Farbw. Hoechst, D. R. P., 76,433.

It will thus be seen that the tropeines derived from tropine itself have a strong mydriatic action, but only a weak anæsthetic action, while their stereo-isomerides, derived from pseudo-tropine, have no mydriatic action, but are powerful local anæsthetics.

Pseudo-tropine is obtained from tropine by heating it with sodium amylate,[4] and it is also obtained from tropinone—



by electrolytic reduction in acid solution.[5]

It should be pointed out that tropinone is obtained by oxidizing tropine with chromic acid,[6] or with permanganate in cold strong acid[7] solution, or with other oxidizing agents.[8] Pseudotropine is then easily converted into tropacocaine by means of benzoyl chloride.

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[1] Giesel, *Pharm. Ztg.* (1891), 149.

[2] Chadbourne, *B. M. J.* (1892), 402.

[3] Liebermann, *Ber.*, **24** (1891), 2336, 2587; **25** (1892), 927.

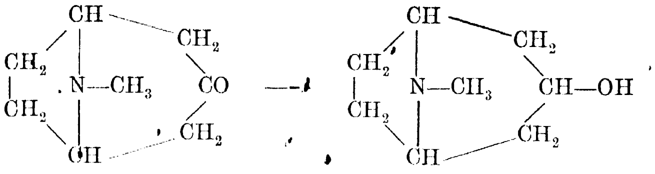
[4] D. R. P., 88,270.

[5] *Ibid.*, 115,517.

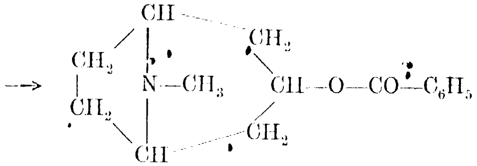
[6] Willstätter, *Ber.*, **29** (1896), 396.

[7] D. R. P., 117,6[illegible]

[8] *Ibid.*, 117,629, 117,630, 118,607.

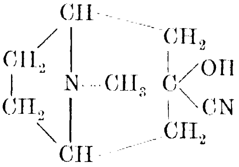


Tropinone. Pseudo-tropine.

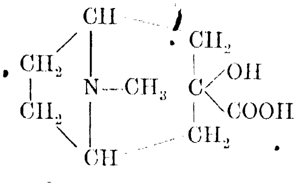


Tropacocaine.

By the action of HCN on tropinone, Willstätter[1] obtained the cyanhydrin—



which on hydrolysis yielded—



which only differs from ecgonine in having the carboxyl group and the hydroxyl group united to the same carbon atom. He termed this substance *α-ecgonine*, and from it he prepared by benzoylation and methylation a substance, *α-cocaine*—

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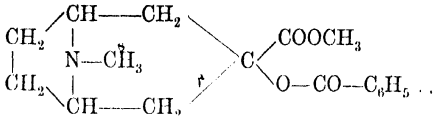
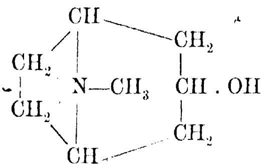
[1] Willstätter, *Ber.*, 29 (1896), 1575, 2216.

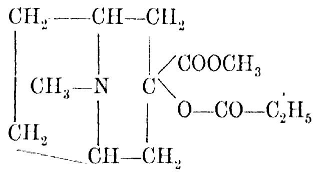


which is, as would be expected from its close structural relation to it, very much like cocaine itself in its chemical properties, such as the cystallizing power of its salts, but strangely enough, it is totally devoid of anæsthetic properties.

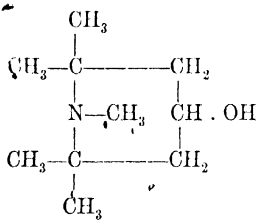
Although α-cocaine does not possess anæsthetic properties, a similar α compound derived from N-methyl-triacetone-alkamine was found to be a valuable local anæsthetic.



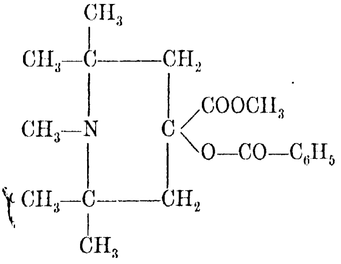
Tropine.



α-cocaine.



N-methyl-triacetone-alkamine.



α-eucaine.

The substance in question is known as *α-eucaine*, and was obtained by Merling in the following manner.[1] Three molecules of acetone were allowed to react with one of ammonia, giving triacetonamine, which on treatment with HCN yields the anhydrin. This on hydrolysis yields triacetone-alkamine-xylic acid, which on benzoylation and methylation yields yl-benzoyl-triacetone-alkamine-carboxylic acid methyl ucaine).

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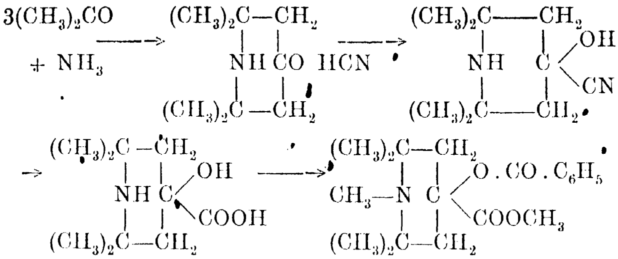
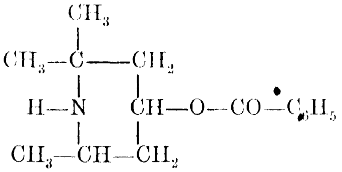
rling, *Ber. deut. Pharm. Gesellschaft*, 6 (1897), 173.



This substance is a cheap substitute for cocaine, and it has the advantage of being less toxic and of being stable to boiling water, so that its solutions can be sterilized by boiling. It has the drawback of being somewhat painful and irritant when injected, and it has now been superseded by *β-eucaine*,[1] the hydrochloride of benzoyl-vinyl-diacetone-alkamine—



This substance is stable to boiling water and so can be readily sterilized. It is less toxic than *α-eucaine*, and is easily soluble in water, the lactate, which is often used instead of the hydrochloride, being soluble up to 30 per cent. It is equal to cocaine in its anæsthetic properties, and is widely used in many branches of surgery. Vinyl-diacetonamine, the parent substance of β-eucaine, was obtained by Harries by the interaction of diacetonamine and acetaldehyde,[2] but it is obtained in better yield by boiling the acid oxalate of diacetonamine with diethylacetal in alcoholic solution.[3]

The vinyl-diacetonamine, on reduction with sodium amalgam,[4] yields a mixture of the two isomeric (*cis* and *trans*) vinyl-diacetone-alkamines.

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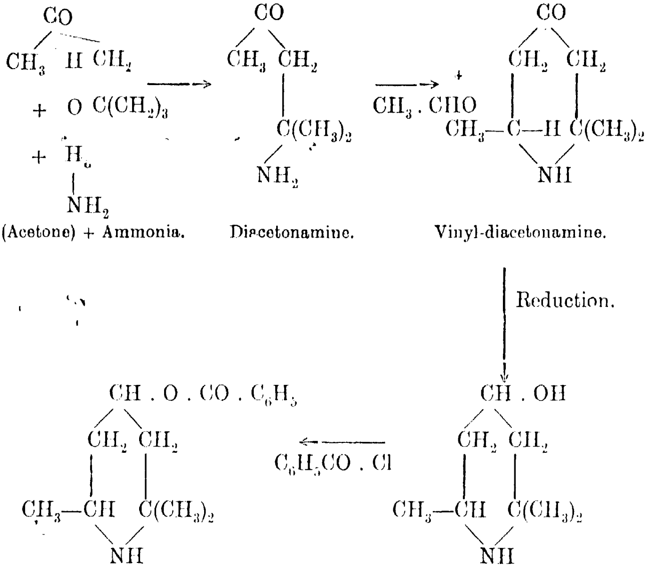
[1] D. R. P., 90,069.

[2] Harries, *Annalen*, **296** (1897), 328; **299** (1898), 346.

[3] E. P., 101,738 (1916).

[4] E. Fischer, *Ber.*, **17** (1884), 1794; Harries, *Annalen*, **294** (1897), 372; D. R. P., 95,622.

This mixture is converted into the stable isomer of lower melting point by boiling with sodium amylate,[1] which is then converted into the base of β-eucaine by treatment with benzoyl chloride.[2]

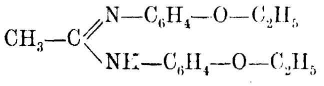


2 (Acetone) + Ammonia. Diacetonamine. Vinyl-diacetonamine.

Reduction.

Base of β-eucaine. Vinyl-diacetone-alkamine.

Besides the members of the cocaine series and the acetone-alkamines, there are a large number of other substances possessing local anæsthetic properties. Many of the antipyretics of the aniline type have this property, and in the case of phenetidine derivatives, the anæsthetic character of the substance is greatly enhanced by combination with a second base. *Holocaine*, one of the best known substances of this type, is the mono-hydrochloride of—



$$CH_3{-}C\begin{cases} {=}N{-}C_6H_4{-}O{-}C_2H_5 \\ {-}NH{-}C_6H_4{-}O{-}C_2H_5 \end{cases}$$

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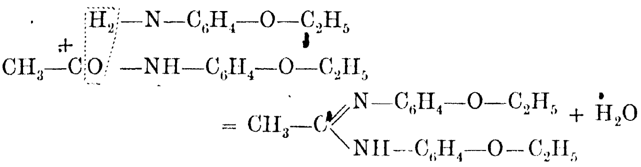
[1] D. R. P., 95,621.

[2] *Ibid.*, 97,672.

It is prepared by condensing phenetidine with phenacetin[1]—

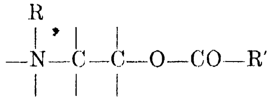


$$\begin{array}{l} H_2\text{—}N\text{—}C_6H_4\text{—}O\text{—}C_2H_5 \\ + \\ CH_3\text{—}CO\ \text{—}NH\text{—}C_6H_4\text{—}O\text{—}C_2H_5 \end{array}$$

$$= CH_3\text{—}C\begin{cases} {}^{\diagup\!\!\diagup} N\text{—}C_6H_4\text{—}O\text{—}C_2H_5 \\ {}_{\diagdown} NH\text{—}C_6H_4\text{—}O\text{—}C_2H_5 \end{cases} + H_2O$$

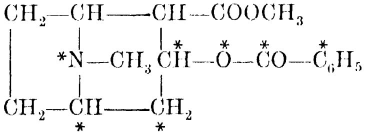
Holocaine has the drawbacks of being more toxic than cocaine, and of being sparingly soluble in water; but, on the other hand, its aqueous solutions keep well, and have a rapid anæsthetic action. It is used in ophthalmic surgery.

In recent years attention has been directed chiefly to alkamine esters, which contain the grouping—

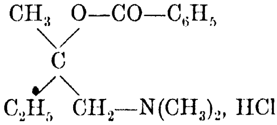


$$\begin{array}{c} R \\ | \quad\ \ | \quad\ \ | \\ \text{—}N\text{—}C\text{—}C\text{—}O\text{—}CO\text{—}R' \\ | \quad\ \ | \quad\ \ | \end{array}$$

a grouping very similar to that indicated by asterisks (*) in the formula for cocaine.[2]



Stovaine, alypine, and novocaine are well-known members of the group. *Stovaine*—



is a well-known synthetic anæsthetic, obtained by the action of magnesium-ethyl-bromide on diethyl-amino-acetone, and benzoylation of the product thus obtained.

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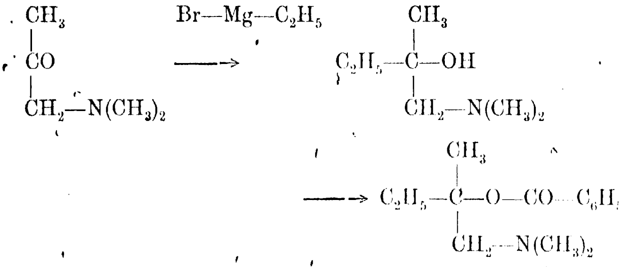
[1] D. R. P., 79,868, 80,568.

[2] Pyman, *J. C. S.*, **93** (1908), 1793.

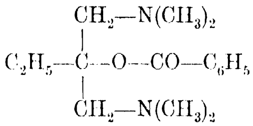


$$\begin{array}{l} CH_3 \\ | \\ CO \\ | \\ CH_2-N(CH_3)_2 \end{array} \xrightarrow{Br-Mg-C_2H_5} \begin{array}{c} CH_3 \\ | \\ C_2H_5-C-OH \\ | \\ CH_2-N(CH_3)_2 \end{array}$$

$$\longrightarrow \begin{array}{c} CH_3 \\ | \\ C_2H_5-C-O-CO-C_6H_5 \\ | \\ CH_2-N(CH_3)_2 \end{array}$$

It is very widely used for producing spinal anæsthesia.

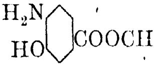
Alypine is the hydrochloride of tetramethyl-diamino-dimethyl-ethyl-carbinyl benzoate—



$$\begin{array}{c} CH_2-N(CH_3)_2 \\ | \\ C_2H_5-C-O-CO-C_6H_5 \\ | \\ CH_2-N(CH_3)_2 \end{array}$$

and is therefore similar to stovaine in its constitution, being the dimethyl-amino derivative of the latter.

As a local anæsthetic, it is said to have the useful properties of cocaine without most of its drawbacks, producing rapid anæsthesia, and being free from injurious effects on the heart and respiration.

A whole series of local anæsthetics which also possess antiseptic properties has been discovered by Einhorn and Heintz.[1] They found that the benzoyl derivative of amino-hydroxy-benzoic ester possessed distinct anæsthetic properties, and contrary to the behaviour of cocaine, the removal of the benzoyl group yielded a substance of which the anæsthetic properties were greater than those of the benzoyl derivative. A large number of substances of this type were produced, of which *p*-amino-*m*-hydroxy-benzoic-methyl-ester,  was introduced into practice under the name of *Orthoform*. It is a white powder, very slightly soluble in water, which is non-

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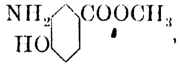
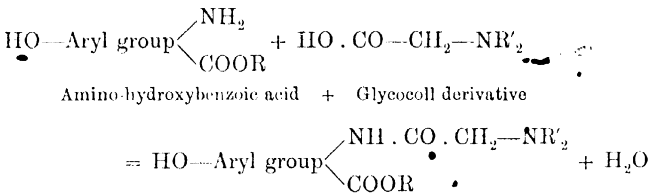
[1] *Münchener med. W.*, **34** (1897), 931; *Annalen*, **311**, 26, 154; **325**, 305; **359**, 145; **371**, 125, 131, 142, 162 (1900-1909).

toxic and has no action on the unbroken skin, but produces anæsthesia on coming into contact with the peripheral nerves themselves. It is used as a dusting powder for painful wounds, etc. The high price of orthoform led to the production of an isomeric substance,



called *New Orthoform*, which has the same physiological action, but is cheaper.[1]

These compounds are not sufficiently soluble to be administered hypodermically, and their more soluble hydrochlorides are too strongly acid for this purpose. To overcome this defect, Einhorn has prepared various derivatives of glycocoll with different amino-hydroxybenzoic acids.

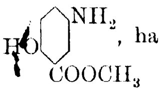


$$\mathrm{HO{-}Aryl\ group}\begin{matrix}\diagup\mathrm{NH_2}\\ \diagdown\mathrm{COOR}\end{matrix} + \mathrm{HO\,.\,CO{-}CH_2{-}NR'_2}$$

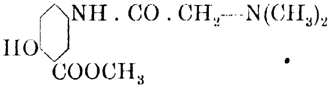
Amino-hydroxybenzoic acid + Glycocoll derivative

$$= \mathrm{HO{-}Aryl\ group}\begin{matrix}\diagup\mathrm{NH\,.\,CO\,.\,CH_2{-}NR'_2}\\ \diagdown\mathrm{COOR}\end{matrix} + \mathrm{H_2O}$$

These compounds differ from the parent substances in being strongly basic, and hence they can form soluble salts (such as hydrochlorides) of neutral reaction. Their anæsthetic action is not closely related to that of the parent substance. A large number of these compounds have been prepared,[2] and the diethyl-glycocoll derivative of



having the formula



has been introduced into therapeutics, in the form of its hydrochloride, under the name of *Nirvanine*.[3] It is easily soluble and is less toxic than orthoform, which it resembles in its general behaviour.

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[1] D. R. P., 97,333, 97,334, 111,932.

[2] *Ibid.*, 106,502, 108,027, 108,871.

[3] *Münchener med. W.*, 49 (1898).

The simplest local anæsthetic of this type is ethyl para-amino-benzoate, $NH_2\langle\quad\rangle COOC_2H_5$, known as *Anæsthesine.* It resembles orthoform in most of its properties, and is said to be free from any toxic action. It is insoluble in cold water, but its solution in olive-oil may be used for hypodermic injection. Its salt with para-phenolsulphonic acid,

$$NH_2 . C_6H_4 . COOC_2H_5, HO . C_6H_4 . SO_3H,$$

is soluble in water, and has been used for hypodermic injection under the name of *Subcutin.*

The isobutyl ester of *p*-amino-benzoic acid

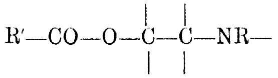
$$NH_2 . C_6H_4 . COOC_4H_9$$

has also been suggested as a local anæsthetic under the name of *Cycloform.*

Novocaine is the hydrochloride of the diethylamine derivative of anæsthesine, having the formula—

$$NH_2\langle\quad\rangle—CO—O—CH_2—CH_2N(C_2H_5)_2,HCl$$

which, it will be seen, contains the previously mentioned grouping—



$$R'—CO—O—\overset{|}{\underset{|}{C}}—\overset{|}{\underset{|}{C}}—NR—$$

It is a non-irritant and powerful local anæsthetic, only one-seventh as toxic as cocaine, and of recent years has found very extended use, so that it is now the most valued of all local anæsthetics.

The preparation of novocaine can be carried out in various ways,[1] but all the methods are somewhat difficult, involving the preparation of ethylene-chlorhydrin and of diethylamine, so that attention has recently been given to improvements in the production of the latter compound.[2]

Ethylene chlorhydrin, for example, may be heated with para-nitrobenzoyl chloride, and the resultant chlorethyl para-nitrobenzoic ester, then heated with diethylamine for twenty-four hours in a closed vessel at 100°-120° C. The diethylaminoethyl ester of para-nitrobenzoic acid so obtained is then reduced with tin and hydrochloric acid to form novocaine.

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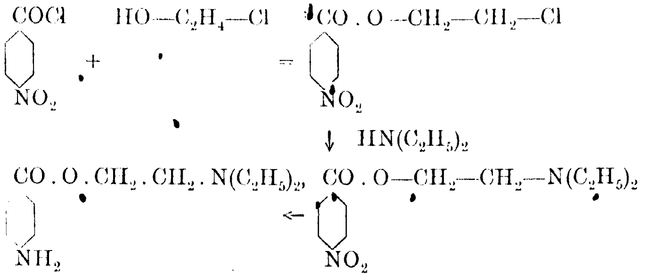
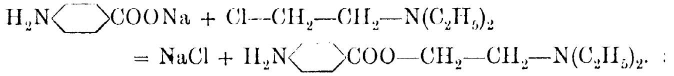
[1] D. R. P., 179,627, 180,291, 180,292; U. S. P., 812,554.
[2] *J. S. C. I.*, **33** (1916), 147; *J. C. S.*, **109** (1916), 174.



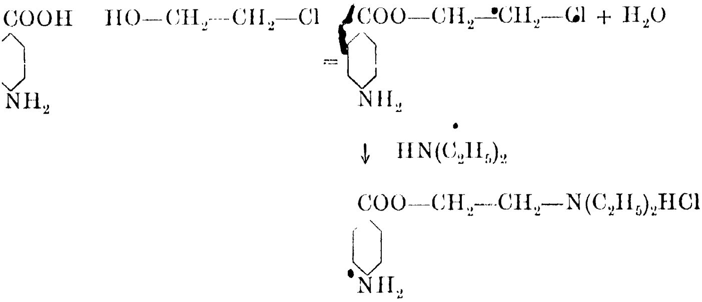
Another method [1] is to condense ethylene chlorhydrin with diethylamine to form chlorethyl-diethylamine.

$$Cl—CH_2—CH_2—OH + HN(C_2H_5)_2 = Cl—CH_2—CH_2—N(C_2H_5)_2 + H_2O.$$

This is then heated with sodium para-aminobenzoate to form the base of novocaine.



In a third variation,[2] para-aminobenzoic acid is condensed with ethylene chlorhydrin by heating them to 100° in sulphuric acid solution. The compound so obtained is then heated in a sealed tube with diethylamine at 100-110° to form novocaine.



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[1] D. R. P., 189,335.

[2] *Ibid.*, 194,748.

CHAPTER VIII.

MORPHINE GROUP AND ISOQUINOLINE GROUPS OF ALKALOIDS.

MORPHINE GROUP.

MORPHINE is the most important of the opium alkaloids, and is the one to which most of the physiological effects of opium are due. The principal alkaloids present in opium may be divided into two well-defined groups :—

(1) *The Morphine Group*, consisting of morphine, codeine, and thebaine, all of them very poisonous substances, and containing a phenanthrene nucleus, as well as a nitrogen ring.

(2) *The Papaverine Group*, consisting of narcotine, papavarine, narceine, laudanosine, oxynarcotine, etc. These substances, which are derivatives of isoquinoline, are far less physiologically active than those of the first group. These alkaloids and some of their derivatives will be considered in the next section, and for the present attention will be directed to the members of the first group.

All the opium alkaloids produce nervous depression, beginning in the psychic centres of the brain, and extending downwards through the various cerebral centres in the reverse order of the development, and they also have a strychnine-like action on the cord, giving rise to convulsions. In some of these alkaloids, such as morphine, the depressant (*i.e.* narcotic and analgesic) action predominates, twitchings or convulsions being extremely rare, while in others, such as thebaine, the convulsant action is far stronger, and practically masks the weak narcotic action. Codeine stands between the two, having marked narcotic properties, but in a weaker degree than morphine, while, on the other hand, it is more liable than morphine to give rise to increased reflexes and spasmodic twitchings.

The following table indicates which of these effects predominates :—[1]

Morphine (most narcotic),
Papaverine,
Codeine,
Narcotine,
Thebaine,
Laudanine (most convulsant).

Morphine has never been synthesized, and its structure is not even known with certainty, so that this section will deal mainly with the efforts that have been made to synthesize derivatives of morphine, which should differ from it in certain respects with regard to their physiological action, and also with the attempts that have been made to obtain synthetic products, which should possess a similar action to morphine owing to the presence of similar groupings in the molecule. These attempts are hampered by the fact that we do not know which portion of the molecule plays the chief part in determining the physiological action.

Nevertheless, it is necessary to indicate the basis on which our knowledge of the structure of morphine rests. The formula of morphine is $C_{17}H_{19}O_3N$; it is a tertiary base, and contains two hydroxyl groups, one of which is phenolic, and the other alcoholic in character. The alkaloid, *codeine*, $C_{18}H_{21}O_3N$, differs from morphine by CH_2, and as it contains *one* hydroxyl group,[2] it therefore appeared probable that it was morphine in which the hydrogen of one of the hydroxyl groups had been replaced by CH_3. This assumption was shown to be highly probable by the work of Matthiessen and Wright,[3] and confirmed in 1881 by Grimaux, who[4] converted morphine into codeine by direct methylation. Therefore the constitution of codeine and that of morphine can be considered together, the former being $C_{17}H_{17}ON(OH)(OCH_3)$, and the latter $C_{17}H_{17}ON(OH)_2$; the complex $C_{17}H_{17}ON$ being the same in both, it is clear that a knowledge of this complex will reveal the structure of both alkaloids.

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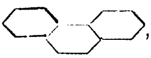
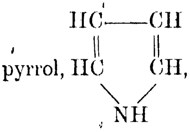
[1] Dixon, "Manual of Pharmacology" (1906), p. 181.
[2] Wright, *J. C. S.*, 27 (1874), 1031.
[3] Matthiessen and Wright, *J. C. S.*, 25 (1872), 506.
[4] Grimaux, *C. R.*, 93 (1881), 591.

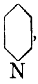
The study of this question has occupied the attention of many chemists, and thanks mainly to the labours of Vongerichten, Schrötter, Knorr, and Pschorr we have gained a tolerably clear insight of the nature of this grouping. Vongerichten and Schrötter by distillation of morphine with zinc dust obtained phenanthrene,



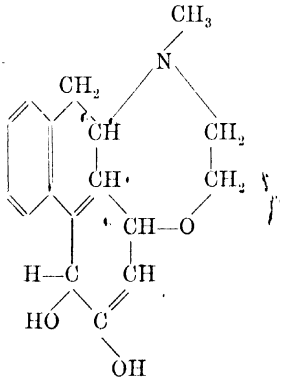
together with pyrrol,

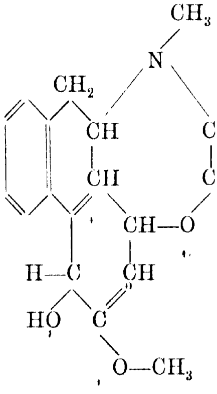


pyridine,



trimethylamine, $N(CH_3)_3$, and ammonia. A detailed account of the numerous investigations that have been carried out on morphine and codeine is beyond the scope of this chapter; an account of the recent work on this subject is given by Dr. H. E. Watt in *Science Progress*, **4**, 279 (1909), and the reader desiring further information is referred to this and to Pictet's "Vegetable Alkaloids." As a result of his own and other investigations, Knorr has suggested the following formula[1] for morphine— that of codeine being—





More recently Knorr has somewhat modified this formula, as shown below, and Pschorr, Jaeckel, and Fecht have suggested a formula for morphine which depicts it as a derivative of N.-methyl-piperidine. This formula is based on a study of apomorphine, $C_{17}H_{17}O_2N$, a dehydration product of morphine.

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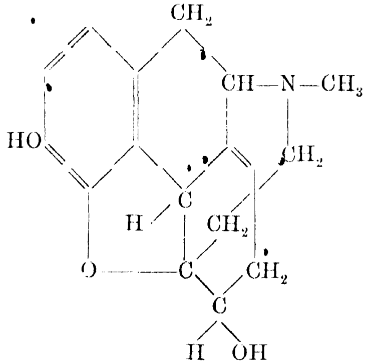
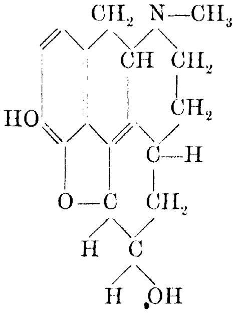
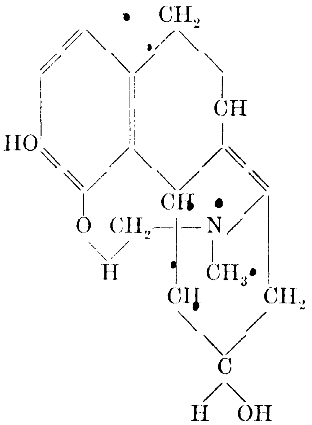
[1] In all cases, an unoccupied corner such as /\ represents /CH\, and |/\ represents |/C\.



Knorr's later formula.



Pschorr's formula.



Bucherer's formula, modified by Knorr.

An important difference between these two formulæ and Knorr's earlier formula is that they show the O and N in separate ring systems. Bucherer's formula, as modified by Knorr, is a link between the two types. In all of these codeine is the same but for the phenolic OH being replaced by OCH_3.

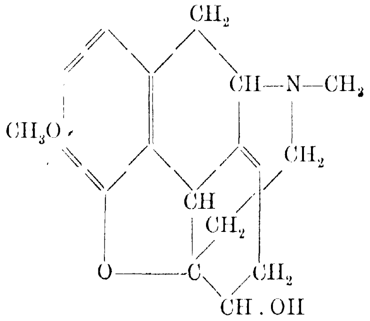
The alkaloid thebaine has been shown by the work of many investigators to be closely related to morphine and codeine,

$(C_{16}H_{14}ONCH_3)(OH)_2$
Morphine.

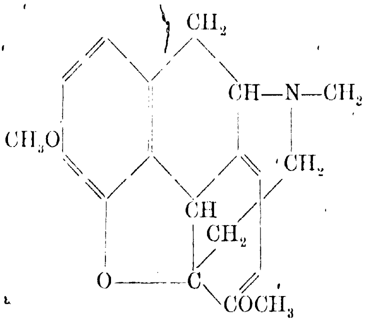
$(C_{16}H_{14}ONCH_3)(OH)(OCH_3)$
Codeine.

$(C_{16}H_{12}ONCH_3)(OCH_3)_2$
Thebaine.

It differs from morphine and codeine in having *both* the hydroxyl groups replaced by methoxy (OCH_3) groups, and in having two atoms of hydrogen less in the rest of the molecule. Accordingly, if we accept Knorr's formula for codeine, we obtain the following formula for thebaine:—



Codeine.



Thebaine.

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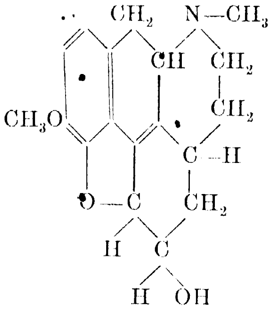
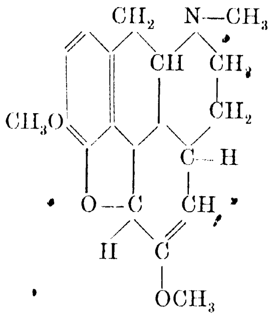
and on the basis of Pschorr's formula for codeine, the corresponding formula for thebaine is as shown below—



Codeine.



Thebaine.

Of the various derivatives prepared from morphine which are used in medicine, the naturally occurring alkaloid codeine is the one which most closely resembles morphine. As already stated, it was first prepared directly from morphine by Grimaux,[1] who also prepared ethylmorphine (codethyline), but since then many other manufacturing methods have been devised in order to obtain better yields. It was first prepared on a large scale by Knoll,[2] and Pechmann's method of methylation by means of diazo-methane[3] has also been applied to the preparation of codeine from morphine,[4] but by this method also the yields do not appear to be very satisfactory. Methyl sulphate is at the present time a favourite methylating agent, and Merck has devised a means of preparing codeine by the action of methyl sulphate on morphine in the presence of alcohol and sodium.[5] The neutral alkyl esters of phosphoric and nitric acids can also be used in the same way as the sulphate.[6]

The pharmacology of morphine, codeine, monacetyl-,diacetyl-, and benzoyl-morphine has been investigated by Stockman and Dott,[7] and that of the homologues of codeine, together with a large number of morphine derivatives by Mering.[1] The action of the higher homologues of codeine is similar to but somewhat weaker than that of codeine itself. Codeine methyl bromide, $C_{18}H_{21}O_3NCH_3Br$, or *Eucodeine* is said to be less toxic than codeine. Ethyl morphine is somewhat exceptional in having a stronger and more prolonged action than codeine, and is recommended against irritant coughing. Its hydrochloride has been introduced into therapeutics under the name of *Dionine*. The benzyl ($C_6H_5—CH_2$) derivative of morphine also resembles codeine in its action, and has been introduced by Mering in the form of its hydrochloride, under the name of *Peronine*. It is obtained by the action of sodium ethoxide and benzyl chloride on morphine in alcoholic solution.[2]

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[1] Grimaux, *C. R.*, **92** (1881), 1140, 1228; **93** (1881), 67, 217, 591.

[2] D. R. P., 39,887.

[3] *Ber.*, **27** (1894), 1888; **28** (1895), 855, 1624.

[4] D. R. P., 95,644, 95,145.

[5] *Ibid.*, 102,634.

[6] *Ibid.*, 107,225, 108,035.

[7] Stockman and Dott, *B. M. J.* (1881), 24th Jan. (1890), II. 189; *Proc. Roy. Soc. Edinb.*, **17** (1890), 321.

The carbonic acid esters of morphine are very unstable, but the acyl derivatives are quite stable, and some of them have attained great practical importance. The acyl derivatives of morphine, in which only the phenolic hydrogen is replaced, mono-acetyl-, propionyl- and benzoyl-morphines closely resemble morphine itself in their physiological action, being intermediate between it and the diacetyl compounds to be described later. (It should be pointed out that in the case of codeine, dionine, and peronine, it is also the hydrogen of the *phenolic* hydroxyl which is replaced by CH_3, C_2H_5 and $C_6H_5 . CH_3$ respectively. These are phenolic *ethers* containing the group —OR, but monoacetyl-, propionyl-, and benzoylmorphine are phenolic *esters*, containing the group O—CO—R, and are more readily hydrolyzed than the *ethers*.) The derivatives of morphine, in which *both* hydroxyl groups are esterified by acid radicles, have also been investigated by Mering. He investigated the diacetyl, di-propionyl, di-isobutyryl, and divaleryl derivatives, and found, in confirmation of the work of Stockman and Dott, that these possessed a more decided narcotic action on dogs than codeine, and a stronger tetanic action than morphine. Clinically, they have proved valuable in lowering reflex irritability and calming spasmodic coughing, but in checking pain they are less active than morphine. Under the names of *Heroin* and *Acetomorphine*, the diacetyl derivative has attained considerable practical importance in checking coughing arising from irritation, etc.

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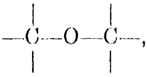
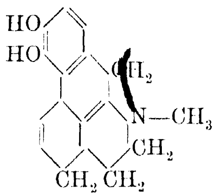
[1] Mering, *Merck's Jahresber.* (1898), 5.

[2] D. R. P., 91,813.

By the action of dehydrating agents, such as concentrated HCl at 140° C., on morphine, a substance is formed which differs from morphine by the elements of water, and is called *apomorphine*, $C_{17}H_{19}O_3N - H_2O \rightarrow C_{17}H_{17}O_2N$. It differs very greatly from morphine in its physiological action, being a most powerful emetic, and in large doses stimulating the respiratory centre, with consequent quickening of the rate of breathing. Its action is therefore quite different from that of morphine. The emetic action of this substance is not local, but is of central-nervous origin through stimulation of the medulla. In therapeutics the hydrochloride is usually used, and is given hypodermically, the dose being soon followed by vomiting without harmful by-effects. The fact that apomorphine can be given in this manner constitutes one of its chief advantages over the peripheral emetics, which act locally on the alimentary canal.

With regard to the chemical nature of apomorphine, it was first thought that one of the oxygen atoms was present in a hydroxyl group, and the other in an ether group,  $-\overset{|}{\underset{|}{C}}-O-\overset{|}{\underset{|}{C}}-$, as only a mono-acetyl derivative had been prepared,[1] but Pschorr, Jaeckel, and Fecht have shown that both oxygen atoms are present as hydroxyl groups.[2]



They also prepared a monomethyl ether of apomorphine, which has been shown[3] to be identical with the so-called "pseudo"-apocodeine, obtained by heating codeine with anhydrous oxalic acid at 150° C.[4]

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[1] Dankwortt, *Annalen*, **228** (1885), 572.

[2] *Ber.*, [illegible]

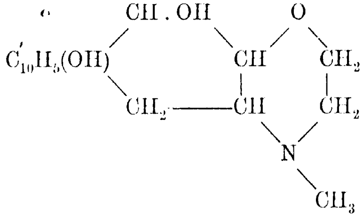
[3] Knorr and Raabe, *Ber.*, **41** (1908), 3050.

[4] *Ber.*, **40** (1907), 3355.

Apocodeine, codeine, apomorphine, and morphine all produce purgation in dogs and cats, but this action is greatest in apocodeine, and diminishes in the order given down to morphine. In the case of apocodeine, the purgative action is greater than the vomiting, and it is stated, when given hypodermically in suitable doses, to produce purgation without vomiting, and its use as a hypodermic purgative has been suggested by Dixon.[1] Such a substance is greatly needed, and should apocodeine come into use for this purpose, it would be one of the most important of artificial drugs.

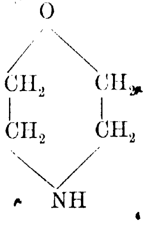
The endeavours that have been made to synthesize substances analogous to morphine do not appear to have been very successful. This is not surprising considering that, apart from any doubt as to the actual constitution of morphine, there is still no means of judging which part of the molecule is most intimately connected with the action of the substance.

The early work of Knorr led him to the conclusion that morphine might be represented by the formula—



a conclusion which was subsequently disproved by his own work.

Knorr gave the name "morpholine" to the grouping—



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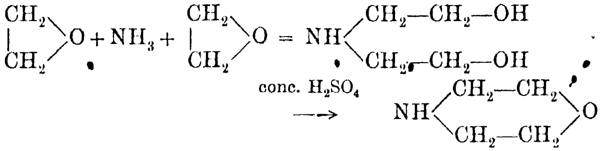
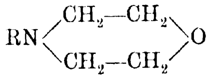
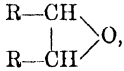
[1] Dixon, *B. M. J.*, 18th Oct., 1902.

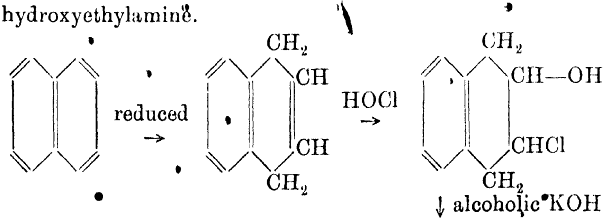
as he regarded it as the parent substance of morphine. A general method of preparing morpholine and its derivatives which was devised by Knorr,[1] consists in splitting off water from dihydroxyethylamines by means of condensing agents, such as 70 per cent. sulphuric acid, acetic anhydride, etc. The dihydroxyethylamines are prepared by the condensation of ethylene-oxide with amines.



The parent substance, morpholine itself, was prepared in this way, using HCl at 160° as the condensing agent.[2] By using various primary amines of the type RNH_2 instead of ammonia, substituted morpholines of the type—



may be obtained, and by using substituted derivatives of ethylene-oxide, such as  O, derivatives of morpholine can be obtained, some of which are not unlike morphine in their properties. As an example, tetrahydro-naphthalene-morpholine may be mentioned, as it resembles morphine most closely.[3] It was obtained by condensing an alicyclic derivative of ethylene-oxide, namely, tetrahydro-naphthylene-oxide with hydroxyethylamine.



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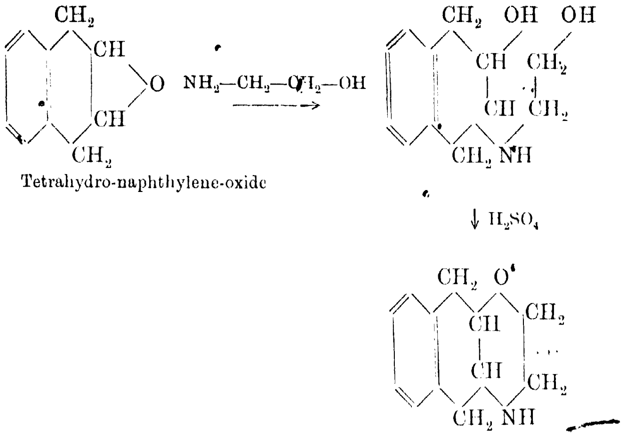
[1] Knorr, *Ber.*, **30** (1897), 909; **31** (1898), 1070, 1969; D. R. P., 95,854.

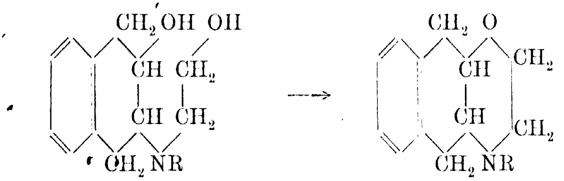
[2] *Ber.*, **22** (1889), 2081.

[3] *Annalen*, **301** (1898), 1; **307** (1899), 171, 187; *Ber.*, **32** (1899), 732.

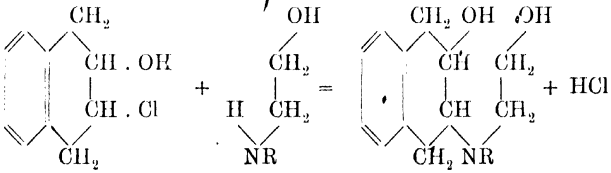


Tetrahydro-naphthylene-oxide

Another method of preparing derivatives of tetrahydronaphthalene-morpholine which has been devised by Knorr[1] is by means of the action of hot dilute sulphuric acid on the hydramines of the naphthalene series.



These hydramines can be obtained by the action of the ethanolamines on the chlorhydrin (see above), or on the oxide of dihydronaphthalene.



A somewhat different method of obtaining a morpholine derivative has been devised by Störmer,[2] and consists in reducing a boiling alcoholic solution of ortho-nitro-phenacetol with tin and hydrochloric acid, whereby 2-methyl-pheno morpholine is obtained.

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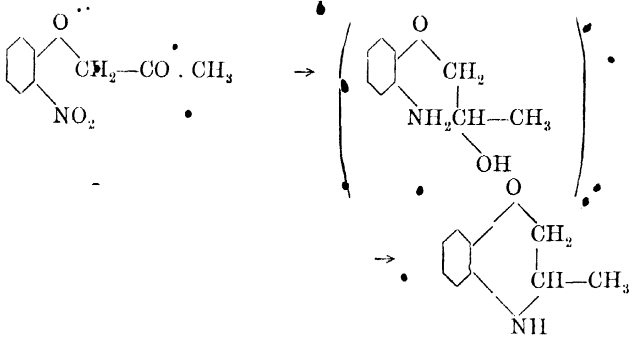
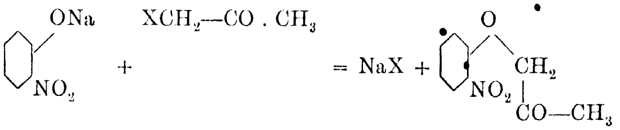
[1] D. R. P., 105,498.

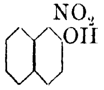
[2] *Annalen*, **288** (1895), 89.



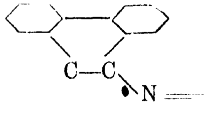
Nitro-phenacetol is obtained by the action of a mono-halogen ketone on the sodium salt of o.-nitrophenol.[1]



In a similar way a naphtho-morpholine may be obtained from—



On the other hand, Vahlen[2] differs from Knorr, and considers that it is the phenanthrene portion of the molecule which is of greatest importance in determining the physiological action of morphine. (Overton has shown that phenanthrene itself has a narcotic action on tadpoles.) Vahlen considers that the "pharmacophore" of morphine is the grouping—



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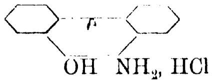
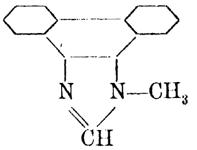
[1] D. R. P., 97,242.

[2] Vahlen, *A. e. P. P.*, 47 (1901), 368.

and he prepared the hydrochloride of 9-amino 10-hydroxyphenanthrene—



which he called "morphigenine," and from this he obtained "epiosine"—



by heating it with sodium acetate, alcohol, and methylamine under pressure. Epiosine, which to a certain extent resembles morphine and codeine in some of its physiological effects, is identical with methyl-diphenylene-iminazole, which has also been prepared by other investigators.[1]

Isoquinoline Alkaloids and their Derivatives.

The most important of the opium alkaloids have already been dealt with, but there are several others of some importance, most of which are derivatives of isoquinoline. These include narcotine, papaverine, narceine, laudanosine, and laudanine. The physiological action of these alkaloids is generally not so marked as that of the members of the morphine group. The important alkaloids of *Hydrastis canadensis*, namely, hydrastine, berberine, and canadine, are also derivatives of isoquinoline, as also is corydaline, the chief alkaloid present in *Corydalis cava*. Of these various alkaloids, hydrastine is probably the most important from the medical point of view, but various artificial alkaloids have been prepared from many members of this series by simple processes such as oxidation, many of which are of considerable therapeutic importance (*e.g.* cotarnine).

In considering these alkaloids, it will be found that our knowledge of their constitution is far more satisfactory than that of the alkaloids of the morphine group. In the majority of cases, not only is the constitution known with a high degree of certainty, but in recent years it has, in many cases, been confirmed by the synthesis of the alkaloid.

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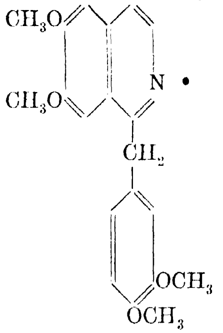
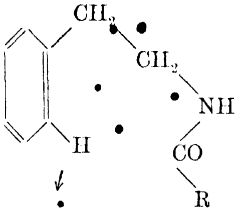
[1] Japp and Davidson, *J. C. S.*, **67** (1895), 1; Zincke and Hof, *Ber.*, **12** (1879), 1644.

Of the alkaloids of this group found in opium, *narcotine* and *papaverine* are present in the largest quantities. The constitution of the latter has been determined chiefly by the work of Goldschmidt,[1] which leaves no doubt that the structure of this alkaloid is represented by the formula—

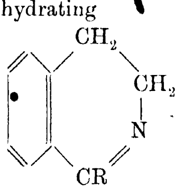


This has been confirmed by the brilliant synthesis of papaverine by Pictet of Geneva.[2]

Pictet had already shown[3] that substances of the type—



on treatment with dehydrating agents, lose a molecule of water, giving dihydro-isoquinoline derivatives of the type—



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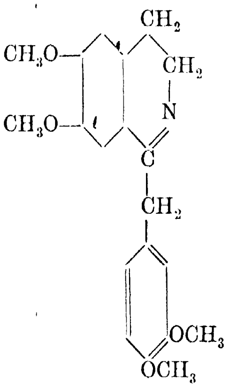
[1] *Monatsh.*, **4**, 714; **6**, 372, 667, 954; **7**, 485; **8**, 510; **9**, 42, 327, 349, 762, 778; **10**, 156, 673, 692; **13**, 697; **17**, 491 (1883-1896).

[2] Pictet and Gans, *Ber.*, **42** (1909), 2943; *C. R.*, **149** (1909), 210.

[3] Pictet and Kay, *Ber.*, **42** (1909), 1973.

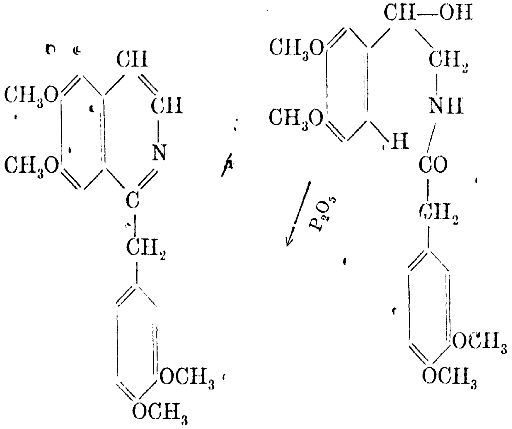
In this way he succeeded in obtaining dihydro-papaverine[1]—



but this cannot be converted into papaverine by oxidation, as any attempt to do this leads to the disruption of the whole molecule. Papaverine could not be obtained directly by using $(CH_3O)_2C_6H_3 . CH{=}CH . NH_2$ instead of—

$$(CH_3O)_2C_6H_3 . CH_2 . CH_2 . NH_2$$

at the beginning of the synthesis, as the former substance is too unstable for this purpose. The difficulty was finally overcome by preparing—



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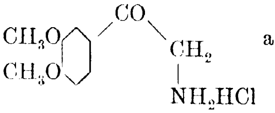
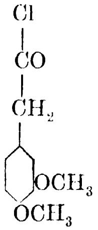
[1] Pictet and Finkelstein, *C. R.*, **148** (1909), 925.

which on treatment with phosphorus pentoxide in xylene solution loses *two* molecules of water with the formation of papaverine. The product thus obtained was in every way identical with papaverine obtained from opium. The first stages of the synthesis are concerned with the preparation of—

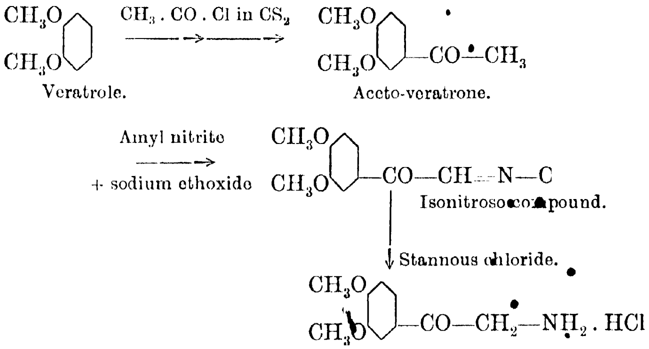


and



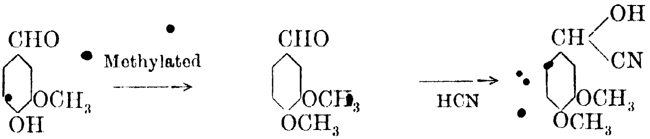
Hydrochloride of amino acetoveratrone. Homoveratroyl chloride.

The first mentioned is prepared according to the following scheme:—

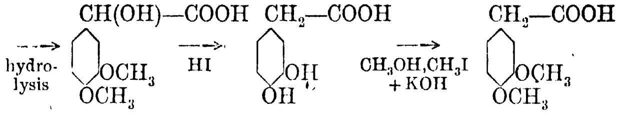


Aminoaceto-veratrone hydrochloride.

The starting-point of the other half of the synthesis is vanillin—

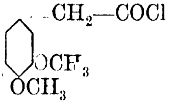


Vanillin. Veratraldehyde.

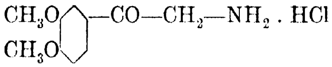


Homoprotocatechuic acid. Homoveratric acid.

This homoveratric acid, treated with PCl_5, yields the chloride—

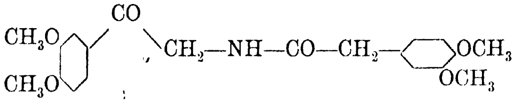


This on shaking with—

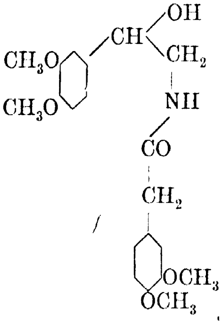


Amino-aceto-veratrone hydrochloride.

in cold potash solution gives, by loss of HCl—



which by reduction with sodium amalgam in alcohol yields—



which on dehydration gives papaverine, as previously described.

Papaverine has only a slight narcotic action, being intermediate in this respect between morphine and codeine.[1] According to Bernard,[2] the chief opium alkaloids stand in the following order in regard to their power of causing convulsions: thebaine, papaverine, narcotine, codeine, and morphine. Of these, thebaine is the only one producing strong tetanic convulsions. Of the alkaloids not mentioned in this list, laudanosine and laudanine have this property strongly marked, the former being slightly less and the latter slightly more active than thebaine itself in this respect.

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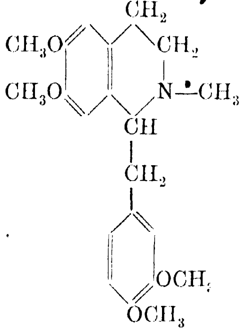
[1] Schröder, *A. e. P. P.*, 17 (1883), 96.
[2] Bernard, *C. R.*, 59 (1864), 406.

Laudanosine closely resembles papaverine in its structure, being the methyl derivative of tetra-hydro-papaverine.



This was shown by Pictet and Athanescu,[1] who obtained it by the reduction of the metho-chloride of papaverine with tin and hydrochloric acid, and resolution of the racemic compound thus obtained with quinic acid. The dextro-compound was found to be identical with laudanosine. It has also been obtained by the reduction of papaverine to tetrahydro-papaverine, and methylation of the latter,[2] but its complete synthesis, which has been recently accomplished by Pictet and Finkelstein,[3] is of greater interest. Dihydro-papaverine was synthesized by Pictet's general method for the preparation of this type of isoquinoline base (*cf.* previous pages), and the metho-chloride of this compound gave by reduction racemic laudanosine, which was then resolved as described above. This synthesis was carried out a short while before that of papaverine, and was therefore the first complete synthesis of an opium alkaloid.

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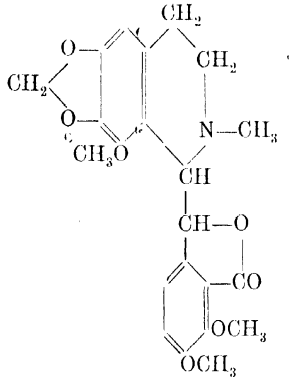
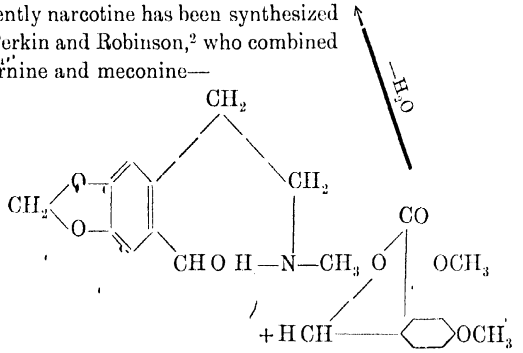
[1] *Ber.*, **33** (1900), 2346; *C. R.*, **131** (1900), 689.
[2] Pyman, *J. C. S.*, **95** (1909), 1610.
[3] Pictet and Finkelstein, *C. R.*, **148** (1909), 295.

Narcotine and its decomposition products have provided material for an enormous number of researches. These are too numerous to be described here, but they point to the probability of the structure shown in the accompanying formula.[1]



Recently narcotine has been synthesized by Perkin and Robinson,[2] who combined cotarnine and meconine—



Cotarnine. Meconine.

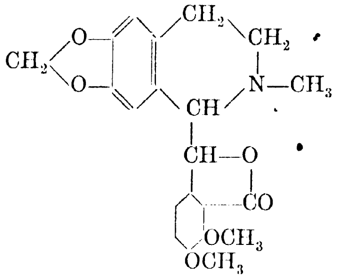
thereby obtaining racemic narcotine (gnoscopine), which was then resolved into its optically active constituents. Meconine was synthesized by Fritsch[1] in 1898, and the synthesis of cotarnine has very recently been accomplished by Salway,[2] so that the synthesis of narcotine is now complete.

---

[1] The positions of the methoxyl, (OCH_3), and piperonyl, $CH_2{<}^{O-}_{O-}$, groups were doubtful, but have been finally established by Freund and Oppenheim, *Ber.*, **42** (1909), 1084.

[2] Perkin and Robinson, *Proc. Chem. Soc.*, **26** (1910), 46 and 131.

The physiological action of narcotine is similar to that of morphine, but less intense. Chemically it is closely related to *hydrastine*, the alkaloid to which the physiological action of *Hydrastis canadensis* is chiefly due. This latter alkaloid, which is an astringent and styptic, is used in uterine hæmorrhage, etc. It was first isolated in a pure condition by Perrins in 1862,[3] and the first observations bearing on its structure were made by Power[4] in 1884. Since then the numerous investigations of Freund and of Schmidt have fully established the structure of this alkaloid. They have shown that it is represented by the formula—

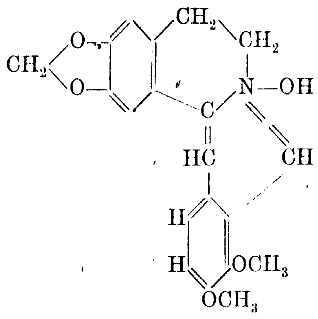


which only differs from that of narcotine by the absence of one methoxy group.

The alkaloid present in largest quantities in *hydrastis* is *berberine*, but its physiological action is not very marked, and hence it does not play so important a part as hydrastine. It is also found in a large number of other plants, and was first discovered in 1826 in the bark of the prickly ash.[5] It has the formula $C_{20}H_{17}NO_4 + H_2O$, and the work of W. H. Perkin, jun., and others indicates that the probable formula of the substance is as shown.[6]

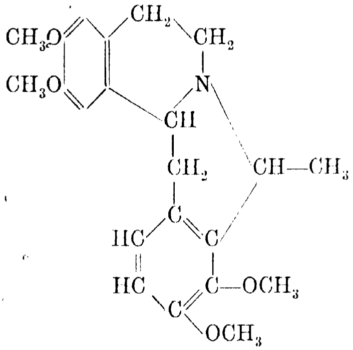
---

[1] Fritsch, *Annalen*, **301** (1898), 351.
[2] Salway, *J. C. S.*, **97** (1910), 1208.
[3] *Pharmaceutical Journal* [2], **3** (1862), 546.
[4] *Ibid.* [3], **15** (1884), 297.
[5] Chevalier and Pelletan, *Journal de Chimie Medicale*, **2** (1826), 314.
[6] Perkin and Robinson, *J. C. S.*, **97** (1910), 305.



Berberine.

This is related to that of hydrastine and narcotine, and is still more closely related to that of corydaline, the chief alkaloid in *Corydalis cava*. *Corydaline* was discovered in 1826 by Wackenroder,[1] and the formula shown herewith was suggested for it by Dobbie and Lauder.[2]



An alkaloid which may be regarded as an isoquinoline derivative, although it does not actually contain the isoquinoline ring, is *narceine*. It is found in opium, but does not have a well-marked physiological action. It can be obtained from narcotine by heating the metho-chloride of the latter with alkali.

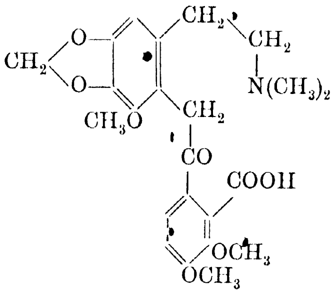
$$C_{22}H_{23}O_7N,CH_3Cl + NaOH = NaCl + C_{23}H_{27}O_8N.$$

---

[1] *Berz. Jahresb.*, **7** (1828), 220.

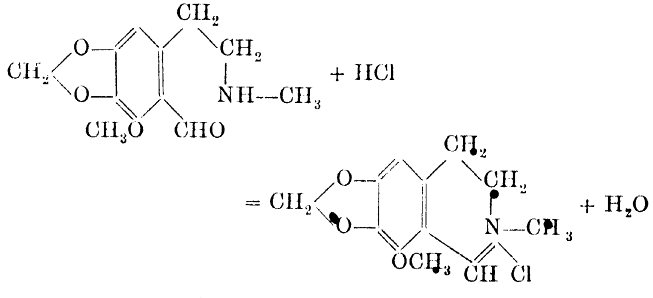
[2] *J. C. S.*, **83** (1903), 605.

This fact led Freund and Frankforter[1] to suggest the formula—



for narceine, which indicates that it is formed from narcotine by the rupture of both the lactone and the pyridine rings.

One of the most important "artificial alkaloids" that are obtained from the true alkaloids of the isoquinoline series is cotarnine. It was first obtained, together with opianic acid, by Wöhler[2] in 1844, by the oxidation of narcotine with manganese dioxide and sulphuric acid. This substance resembles narceine in the fact that in the free base the pyridine ring is opened out, but in the salts which are formed with elimination of water, the ring closes and derivatives of di-hydro-isoquinoline are formed.



There is some evidence that the free base also exists as an isoquinoline derivative of this quaternary ammonium form when dissolved in alcohol.[3] This alkaloid is of importance in medicine as a styptic and as a uterine sedative, and has been brought into the market under the name of "*Stypticine*," and its phthalic acid salt under the name of "*Styptol*."

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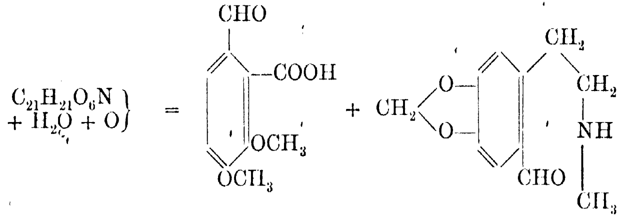
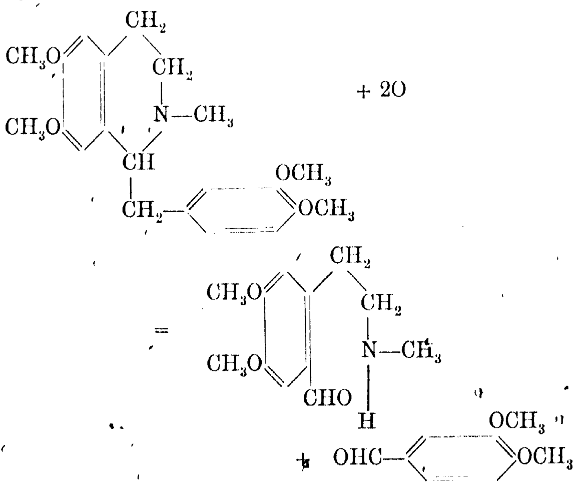
[1] *Annalen*, 277 (1893), 20.
[2] *Ibid.*, 50 (1844), 1.
[3] Dobbie, Lauder, and Tinkler, *J. C. S.*, 83 (1903), 598.

Hydrastine, on oxidation with MnO_2 and H_2SO_4, behaves in a very similar way to narcotine, yielding opianic acid and a basic substance, *hydrastinine*, which corresponds to *cotarnine*—



Physiologically, hydrastinine resembles cotarnine very closely.

It has been shown by Pyman,[1] that laudanosine, on oxidation with MnO_2 and H_2SO_4, behaves in a precisely similar way to narcotine and hydrastine. The products are a basic substance, 4-5 dimethoxy-2 β methylaminoethyl-benzaldehyde, and veratraldehyde, the former being analogous to cotarnine and hydrastinine, and the latter corresponding to opianic acid.



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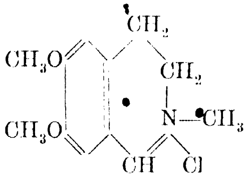
[1] Pyman, *J. C. S.*, **95** (1909), 1266.

The former combines with acids to form salts of the isomeric iso-quinolinium hydroxide, in just the same way as do cotarnine and hydrastinine.

Of these, the chloride, which is 6-7 dimethoxy-2 methyl-3-4-dihydro-isoquinolinium chloride, has been introduced into practice under the name "*Lodal*"—[1]

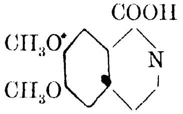


It causes a rise of blood pressure, and renders the heart-beat slower and stronger.

Other pressor substances which have been obtained from isoquinoline alkaloids will be considered in the next chapter.

It is of interest to note that the N-methyl derivatives of tetrahydro-isoquinoline (narcotine, laudanosine, and hydrastine) are convulsant poisons, while those derived from dihydro-isoquinoline (cotarnine, "Lodal," and hydrastinine) are not. This relation does not hold for those derivatives, such as papaverine, which contain no methyl group attached to the nitrogen.

More recently it has been shown[2] that emetine, $C_{29}H_{4\text{[illegible]}}O_4N_2$, and cephaeline, $C_{28}H_{38}O_4N_2$, the chief alkaloids of ipecacuanha, are derivatives of isoquinoline, as the former on oxidation gives 6-7-dimethoxyisoquinoline-1 carboxylic acid,



which is also an oxidation product of papaverine. It was also shown that emetine is the monomethyl ether of cephaeline, the former being $C_{25}H_{28}N_2(OCH_3)_4$, and the latter,

$$C_{25}H_{28}N_2(OH)(OCH_3)_3.$$

These alkaloids have attracted considerable attention recently owing to the valuable effect of emetine hydrochloride in the treatment of amœbic dysentery. It appears to have a specific effect on the protozoal parasites just as quinine has on those of malaria.

---

[1] Wellcome and Pyman, English Patent (1909), 314.

[2] Carr and Pyman, *J. C. S.*, 105 (1914), 1591.

According to Pyman,[1] the protozoacidal effects on this parasite (*Entamœba histolytica*) of emetine, cephaeline, N-methyl-emetine, and N-methyl-cephaeline are practically equal. Various other interesting facts concerning the relation between chemical constitution and physiological action in this field are given in the same paper.

In some cases the use of the double iodide of emetine and bismuth has been found to be more advantageous than that of emetine hydrochloride itself.

Recently two more alkaloids have had their constitution established by Perkin,[2] and shown to be isoquinoline derivatives. These are cryptopine and protopine, both of them occurring in very small quantities in opium; the latter is also obtainable from many other plant sources.

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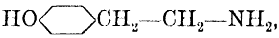
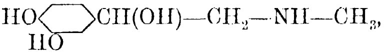
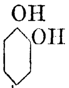
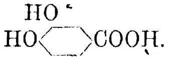
[1] Pyman, *J. C. S.*, **111** (1917), 1127.

[2] *J. C. S.*, **109** (1916), 815.

CHAPTER IX.

ADRENALINE AND OTHER DERIVATIVES OF ETHYLAMINE.

WITHIN recent years, a large number of ethylamine derivatives, possessing powerful physiological action, have been isolated from various plant and animal sources. Many of these are derivatives of para-hydroxyphenylethylamine,  $HO\langle\;\rangle CH_2{-}CH_2{-}NH_2$, and have the property of producing effects very similar to those produced by stimulation of the sympathetic nervous system,[1] one of the most notable of these being rise of blood pressure. Para-hydroxyphenylethylamine is present in aqueous extracts of ergot, and other closely related substances are also found in various plants, but the most important compound of this class is adrenaline,  $HO(HO)\langle\;\rangle CH(OH){-}CH_2{-}NH{-}CH_3$, an active principle which has been isolated from the suprarenal glands. It was first obtained in the impure condition by Abel and Crawford, in 1897,[2] and in a more pure condition as the benzoyl derivative by Abel, in 1899.[3] It was called epinephrine by these investigators, and it was also isolated by von Fürth,[4] who gave it the name suprarenine. The name adrenaline was first given to it by Takamine,[5] who was also the first to obtain it in a crystalline condition. He proposed the formula $C_{10}H_{13}O_3N$ from the results of his analyses, and also made the first observations throwing some light on its constitution, as he obtained substances from it supposed to be catechol and protocatechuic acid,  and .

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[1] Barger and Dale suggest the term "sympathomimetic" to describe this action.

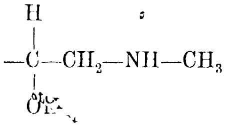
[2] *Zeit. physiol. Chem.*, 28 (1898), 318.

[3] *Amer. Journ. of Physiol.*, 3 (1900), xvii.-xviii.; *Proc. of Amer. Physiol. Soc.* (1898), 3.

[4] Von Fürth, *Zeit. physiol. Chem.*, 29 (1900), 105.

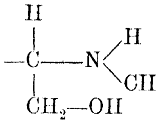
[5] Takamine, *Amer. Journ. Pharm.*, 7[illegible] (1901), 523; *Proc. Physiol. Soc.* (1901), xxix.-xxx.; D. R. P., 131,496.

Shortly afterwards it was isolated by Aldrich by means of a somewhat different method, and he gave to it the formula $C_9H_{13}O_3N$, which is now universally accepted. Abel still preferred the formula $C_{10}H_{13}O_3N,\frac{1}{2}H_2O$, which corresponds to almost identically the same composition as $C_9H_{13}O_3N$, but he brought forward no evidence to show that it contained water of crystallization. Pauly[1] confirmed the formula $C_9H_{13}O_3N$, and suggested that it contained the groupings—

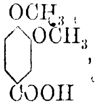


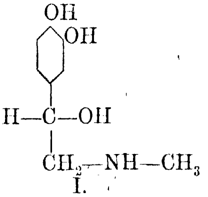
$$-\overset{\displaystyle H}{\underset{\displaystyle OH}{C}}-CH_2-NH-CH_3$$

or

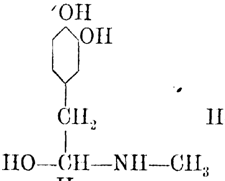


$$-\overset{\displaystyle H}{\underset{\displaystyle CH_2-OH}{C}}-N\begin{matrix}H\\CH_3\end{matrix}$$

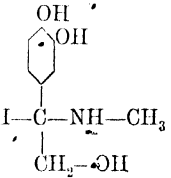
Von Fürth[2] had already suggested the formula $(HO)_2C_6H_3$-$[C_2H_3(OH)NH-CH_3]$, as he had found that it did not contain a methoxy group, and that it yielded methylamine salts on treatment with concentrated acids. Jowett[3] confirmed the formula $C_9H_{13}O_3N$, and from the products of a potash fusion isolated a small quantity of a substance believed to be protocatechuic acid, but obtained more positive evidence by methylation and subsequent oxidation, by which means veratric acid, , was obtained, and he therefore suggested the alternative formulæ—



I.



II.



III.

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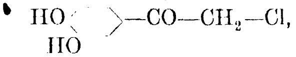
[1] Pauly, *Ber.*, **36** (1903), 2944.

[2] Von Fürth, *Beitr. Chem. Physiol. Path.*, **1** (1901), 243.

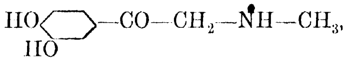
[3] Jowett, *J. C. S.*, **85** (1904), 192.

with a preference in favour of I., which is the formula at present accepted as representing the constitution of adrenaline.

In 1904 Friedmann[1] showed that the benzenesulphonyl derivative of adrenaline on oxidation yielded the corresponding derivative of a ketone *adrenalone*, which he also obtained by the action of methylamine on chloracetyl-catechol—

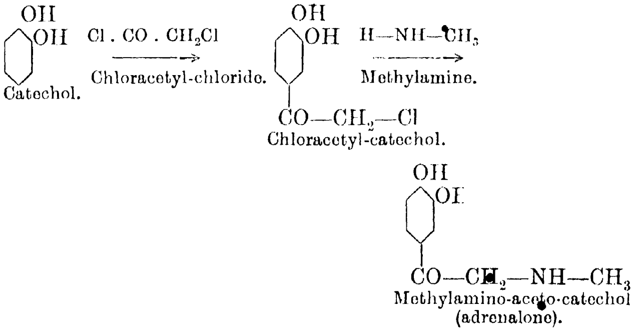


and which, therefore, has the constitution—



and this confirms Jowett's formula for adrenaline.

From this time onwards, the chemical investigations of adrenaline have had as their chief object the synthesis of this important and valuable substance. The adrenalone of Friedmann can be obtained by the action of an excess of methylamine on chloracetyl-catechol, the resultant base being precipitated by ammonia.[2]



The reduction of this ketone to the corresponding secondary alcohol (adrenaline) presented great difficulty, but it was successfully accomplished by electrolytic reduction or by the action of aluminium amalgam on the sparingly soluble sulphate of the ketonic base.[3]

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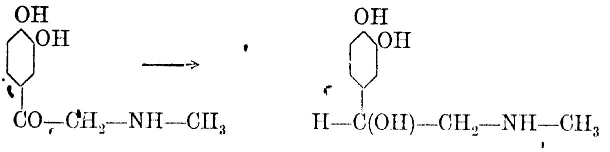
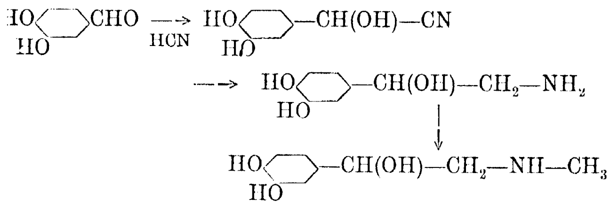
[1] *Beitr. Chem. Physiol. und Pathologie*, 6 (1904), 92

[2] Stolz, *Ber.*, 37 (1904), 4149; D. R. P., 152,814; English Patent (1903), 25,480; Dakin, *Proc. Roy. Soc.*, 76, B (1905), 491.

[3] D. R. P., 157,300; also Dakin, *loc. cit.*



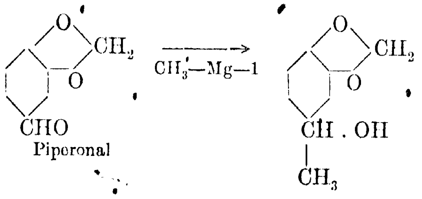
Another method for the synthesis of adrenaline starts from protocatechuic aldehyde. This on treatment with hydrocyanic acid yields the cyanhydrin, which is then reduced to an amine which can be converted to adrenaline by methylation. This method is not used commercially.



The product thus obtained is the racemic form of adrenaline, which is less active than the naturally occurring lævo-rotatory variety.

The resolution of racemic adrenaline into its two optically active components has been accomplished by means of the fractional precipitation of its salts with tartaric acid, and also by means of *Penicillium glaucum*.[1] The synthesis of natural adrenaline is therefore complete.

The methylene and dimethyl ethers of adrenaline have been synthesized by means of a different method,[2] but unfortunately these could not be transformed into adrenaline itself.



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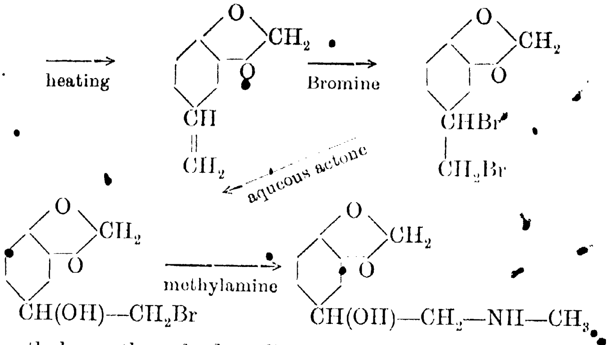
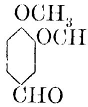
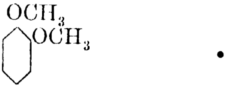
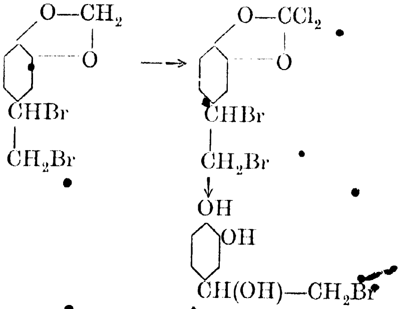
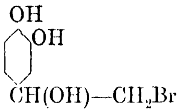
[1] Flächer, *Zeit. physiol. Chem.*, 58 (1908), 185, 189; and also Meister, Lucius, and Brüning, D. R. P., 222,451.

[2] Barger and Jowett, *J. C. S.*, 87 (1905), 967.



The methylene ether of adrenaline thus formed has a physiological action similar to that of adrenaline itself. Similarly veratraldehyde,  was transformed into the dimethyl-ether of adrenaline,  , although this was only obtained as a syrup. Although by the action of phosphorus pentachloride on the methylene ether, Barger and Jowett (*loc. cit.*) were unable to obtain a chlorinated compound which should yield the dihydroxy-compound with water—



Böttcher[1] states that an excess of phosphorus pentachloride gives , which with aqueous methylamine yields a physiologically active base, supposed to be adrenaline. Pauly,[1] however, considers that Böttcher has not proved the formation of adrenaline by this method.

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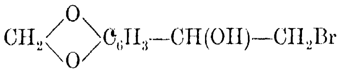
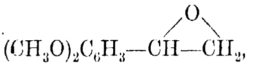
[1] Böttcher, *Ber.*, 42 (1909), 2[illegible]8.

Considerable light has been thrown on this reaction by Mannich,[2] who showed that a mere direct replacement of the halogen by the methylamino group does not take place in chlor- or bromhydrins of the types—



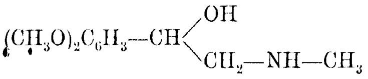
$$CH_2{<}\begin{matrix}O\\O\end{matrix}{>}C_6H_3-CH(OH)-CH_2Br$$

and $(CH_3O)_2C_6H_3-CH(OH)-CH_2Br$. Under the influence of methylamine, hydrobromic or hydrochloric acid is lost, resulting in the formation of an unstable oxide of the type—



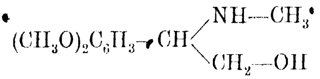
$$(CH_3O)_2C_6H_3-\overbrace{CH-CH_2}^{O},$$

which then reacts with more methylamine to form bases of the adrenaline series, e.g.—



$$(CH_3O)_2C_6H_3-CH{<}\begin{matrix}OH\\CH_2-NH-CH_3\end{matrix}$$

or of the *iso*adrenaline series, e.g.—



$$(CH_3O)_2C_6H_3-CH{<}\begin{matrix}NH-CH_3\\CH_2-OH\end{matrix}$$

Mannich and Jacobsohn[3] succeeded in preparing the methylene and dimethyl ethers of adrenaline in a pure state, and they also obtained the methyl ether of β-methyl-adrenaline by the action of bromine on methyl-isoeugenole.

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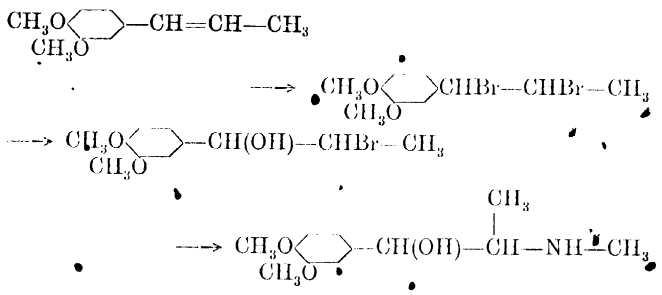
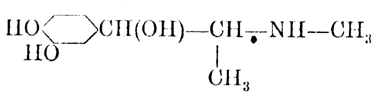
[1] Pauly, *Ber.*, 42 (1909), 484.

[2] Mannich, *Arch. Pharm.*, 248 (1910), 127.

[3] Mannich and Jacobsohn, *Apothek. Zeitg.*, 24 (1909), 60.



This then gives β-methyl-adrenaline—



on treatment with hydriodic acid. According to Kobert this substance has not the physiological action of adrenaline.

Meanwhile an extended physiological investigation of adrenaline was carried out by Elliott,[1] who confirmed and extended the earlier work which Schäfer and Oliver, and Langley had carried out with extracts of the gland. In general, the effect of adrenaline on any structure is similar to that which follows excitation of the sympathetic nerves supplying the tissue. If administered subcutaneously or locally to mucous surfaces, it causes very marked constriction of the blood-vessels, and so arrests bleeding. In moderate doses, subcutaneous injections produce no general systemic effect, very much larger doses being needed to raise the blood pressure by this means.

It is of interest to note that there is a very marked difference in the physiological activity of the naturally occurring lævo-adrenaline and the dextro isomeride, this being one of the very best examples of difference in physiological behaviour between stereo-isomerides. It was shown by Cushny[2] that natural lævo-adrenaline acts approximately twice as strongly in increasing the blood pressure as synthetic racemic-adrenaline, and presumably also on the other organs affected by adrenaline. From this it was inferred that *d*-adrenaline was inactive on these tissues, and this view was apparently confirmed by an examination of partly isolated *d*-adrenaline. The general character of these results was confirmed by other workers,[1] but subsequently Cushny[2] showed that *d*-adrenaline is not quite inert in this respect, but has an activity about one-twelfth of that of *l*-adrenaline, so that the action of *r*-adrenaline is almost entirely due to the *l*-adrenaline contained in it.

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[1] Elliott, *Journ. of Physiol.*, 32 (1905), 401.

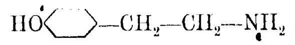
[2] Cushny, *Journ. of Physiol.*, 37 (1908), 130.

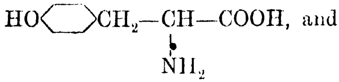
The synthetic racemic mixture can be completely converted into the desired active component. Either the dextro or the lævo compound can be racemized by treatment with acids; the inactive mixture is then resolved into its components, and the isomeride not required can then be again racemized and subsequently resolved, this process being repeated as often as required.[3] The authors of this method state that the dextro compound also possesses valuable therapeutic properties.

The therapeutic uses of adrenaline are very numerous, and a mere list of the references to the literature of this subject would fill pages; an account of many of these publications is given in Merck's Reports during the last fifteen years. Adrenaline is largely used in conjunction with cocaine and eucaine, as it produces a localized anæmia, and so checks bleeding, and it also appears to neutralize the toxic effect of cocaine. The action of adrenaline in producing ischæmia finds application in a variety of complaints, hay-fever being an example.

Adrenaline is also met with under the names of hemisine, surrenine, epinephrine, suprarenine, etc.

Recently various substances chemically related to adrenaline, and to a large extent resembling it in their physiological action, have been isolated from various plant and animal sources. Of these, *para-hydroxyphenylethylamine*,



which may be regarded as the mother substance of the series, is the most important. It was first prepared in small quantities by heating tyrosine,[1]  and it has since been obtained in small quantities from various animal sources. Putrid meat has for some time been known to produce a rise of blood pressure (pressor action), and in 1909 it was found that this action was due to a number of amines,[2] of which para-hydroxyphenylethylamine had the most powerful action. The amines which showed this action in a weaker degree were iso-amylamine, $(CH_3)_2CH—CH_2—CH_2—NH_2$, and phenylethylamine. It is almost certain that these bases are produced in the process of putrefaction by loss of carbon dioxide from the corresponding amino acids :—

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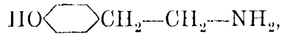
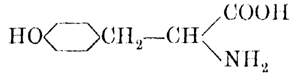
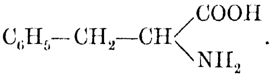
[1] Abderhalden and Müller, *Zeit. physiol. Chem.*, **58** (1908), 185; Abderhalden and Thies, *Zeit. physiol. Chem.*, **59** (1909), 22; Abderhalden and Slavy, *Zeit. physiol. Chem.*, **55** (1908), 129.

[2] Cushny, *Journ. of Physiol.*, 38 (1909), 259.

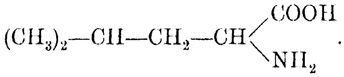
[3] D. R. P., 220,355.

Para-hydroxyphenylethylamine, 

rom tyrosine, 

Phenylethylamine, $C_6H_5—CH_2—CH_2—NH_2$, from phenyl-alanine, 

$C_6H_5—CH_2—CH\genfrac{}{}{0pt}{}{\diagup COOH}{\diagdown NH_2}$.

And isoamylamine, $(CH_3)_2CH—CH_2—CH_2—NH_2$, from eucine, 

$(CH_3)_2—CH—CH_2—CH\genfrac{}{}{0pt}{}{\diagup COOH}{\diagdown NH_2}$.

Putrid placental extracts had also been shown to produce a pressor action,[3] and para-hydroxyphenylethylamine has been solated from such extracts.[4]

The drug ergot has long been used on account of its therapeutic properties, but it is very variable in its activity, and equires to be physiologically standardized owing to the unatisfactory state of our knowledge of the alkaloids present n ergot. Recently, however, a great deal of light has been hrown on the chemistry of ergot by the work of Barger,

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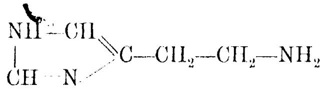
[1] Schmidt and Nasse, *Annalen*, 133 (1865), 214.

[2] Barger and Walpole, *Journ. of Physiol.*, 38 (1909), 343; Dale and Dixon, *ibid.*, 39 (1909), 25.

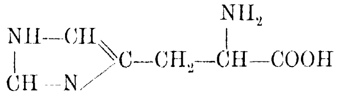
[3] Dixon and Taylor, *B. M. J.*, II. (1907), 1150.

[4] Rosenheim, *Journ. of Physiol.*, 38 (1909), 337.

Dale, and others. The amorphous alkaloid ergotoxine[1] is physiologically active, but it does not possess all the characteristics of the action of ergot, and the small amount of this alkaloid present in most pharmacopœial preparations of ergot led to the postulation of an active principle soluble in water.[2] The physiological properties of para-hydroxyphenylethylamine suggested that it might be the expected active principle, and this expectation was realized when it was shown to be present in aqueous extracts of ergot,[3] and to be the chief cause of their physiological action. Not only has this substance been isolated from ergot,[4] but synthetic methods for its preparation have been devised which have rendered practicable its introduction into therapeutics. These syntheses will be discussed together with those of other compounds of this series, but mention should be made at this point of another base isolated from ergot.[5] This is β iminazolyl-ethylamine—



and it is formed from the amino-acid, histidine—



by loss of carbon dioxide in just the same way as p.-hydroxyphenylethylamine is formed from tyrosine. The action of ergot in producing gangrene of the cock's comb is regarded[6] as being due to the alkaloid ergotoxine, and the rise in blood pressure is attributed to p.-hydroxyphenylethylamine, while the powerful action of ergot in stimulating the isolated uterus to tonic contraction is caused by β iminazolyl-ethylamine. This substance, although it has a very powerful physiological action, differs from all the other active derivatives of ethylamine described in this chapter in causing a lowering instead of a rise of blood pressure.

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[1] Barger and Carr, *J. C. S.*, **91** (1907), 357.

[2] Barger and Dale, *Bio-Chemical Journal*, **2** (1907), 286.

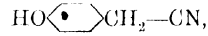
[3] *Ibid.*, *Proc. Physiol. Soc.*, 15th May, 1909.

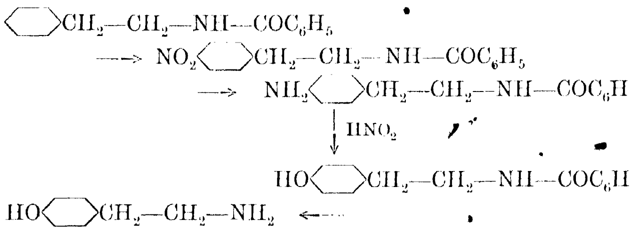
[4] Barger, *J. C. S.*, **95** (1909), 1123; English Patent (1909), 314.

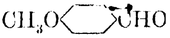
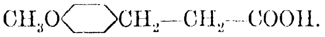
[5] Barger and Dale, *Proc. Chem. Soc.*, **26** (1910), 128; *J. C. S.*, **97** (1910), 2592.

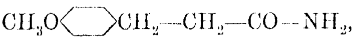
[6] *Ibid.*, *Proc. Physiol. Soc.*, 15th July, 1910, xxxviii.

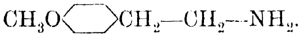
It has been introduced into medicine under the names of *Histamine* and *Ergamine*.

The original method for the synthesis of p.-hydroxyphenylethylamine was by the reduction of p.-hydroxyphenylacetonitrile,[1] , and subsequently two other methods of synthesis were described.[2] One of these is by the nitration of benzoyl-phenylethylamine, reduction of the resulting para-nitro compound to the amine, which yields the benzoyl derivative of the desired product when diazotized in boiling solution. This benzoyl derivative is then hydrolyzed.



The other method starts from anisic aldehyde,  which, by the method of Perkin and Robinson,[3] yields the acid . This is then converted into the chloride, and thence into the amide—



which by the Hofmann reaction is made to yield the amin . By means of strong hydrobromic acid, the methoxy group is converted into hydroxy giving para-hydroxyphenylethylamine.

p.-Hydroxyphenylethylamine has also been prepared from anisaldehyde by Rosenmund,[4] who condensed the latter sub stance with nitromethane to prepare β-nitro-p.-methoxystyrene This is then reduced to p.-methoxyphenylethylamine, which i demethylated with hydriodic acid.

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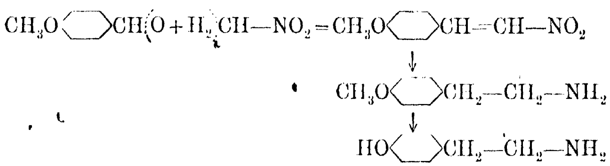
[1] Barger, *J. C. S.*, **95** (1909), 1123; English Patent (1909), 311.

[2] Barger and Walpole, *J. C. S.*, **95** (1909), 1720; English Patent (1909 1561.

[3] Perkin and Robinson, *J. C. S.*, **91** (1907), 1079.

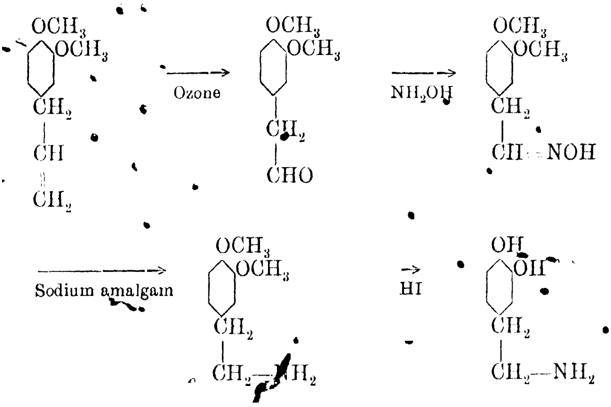
[4] Rosenmund, *Ber.*, **42** (1909), 4778.

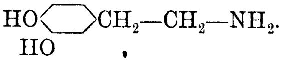


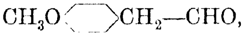
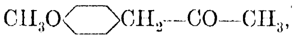
This substance has been introduced into practice under the name of "*Tyramine*" as the chief active pressor principle of aqueous extracts of ergot, and being a pure chemical compound it has the advantage in being certain and uniform in its action.

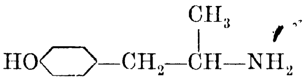
Tyramine and adrenaline are representatives of two important subdivisions of these pressor amines, the former being the simplest member of those derivatives of phenylethylamine containing *one* phenolic hydroxyl group in the para position to the ethylamine group, and the latter being a representative of the compounds containing *two* phenolic hydroxyl groups in the 3-4 position. Many other compounds of this type have been obtained by synthetic methods, and their physiological action determined. The syntheses of some of the most important will now be considered, and the physiological action dealt with subsequently.

The simplest member of the adrenaline series (*i.e.* those with two phenolic hydroxyl groups in the 3-4 position) is 3-4 di-

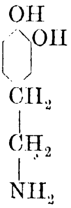


hydroxyphenylethylamine,  This compound has been synthesized[1] from eugenol methyl ether, which by oxidation with ozone in benzene solution in presence of water gives the aldehyde of homoveratric acid. This s converted into the oxime, which on reduction with sodium amalgam and glacial acetic acid yields the dimethyl ether of he desired compound. This ether is then converted into the dihydroxy compound with hydriodic acid in the usual manner.

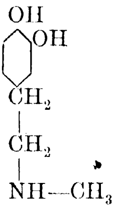
By the reduction of the oximes of other aldehydes and ketones, other members of these two series may be obtained. For example, homoanisic aldehyde,  gives p.-hydroxyphenylethylamine; and para-methoxybenzyl methyl-ketone,  gives, when treated n the same way, p.-hydroxyphenyl-isopropylamine—



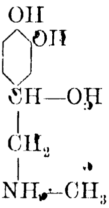
3-4 dihydroxyphenylethylamine (A) differs from adrenaline by the absence of a methyl group attached to the nitrogen and of an aliphatic hydroxyl group on the side chain. An interesting ntermediate compound between these two is 3-4 dihydroxyphenylethylmethylamine (B).



(A)



(B)



Adrenaline.

This, it will be observed, differs from adrenaline only by he absence of the aliphatic hydroxyl group, and it is of interest n being a connecting link between that substance and the pressor derivatives obtained from isoquinoline alkaloids (e.g., Lodal," cf. previous chapter). It differs very little from adrenaline in the qualitative nature of its physiological action, but the rise of blood pressure, although not so intense, is more prolonged. This substance has been introduced into therapeutics under the name of "*Epinine.*" It was obtained from 1-keto-6-7 dimethoxy-2 methyl-tetrahydroisoquinoline[1] by heating it with hydrochloric acid at 170-175°. The reaction probably takes place in the following stages:—

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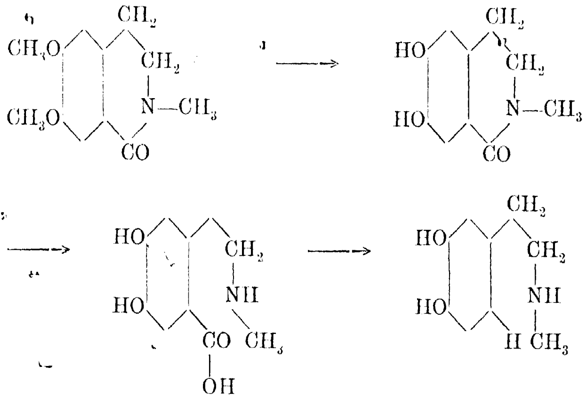
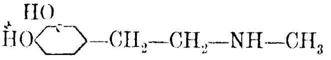
[1] Mannich and Jacobsohn, Ber., 43 (1910), 189.

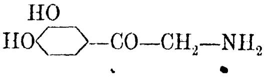




$$i.e.\ \overset{HO}{HO}\!\left\langle\quad\right\rangle\!-CH_2-CH_2-NH-CH_3$$

The corresponding propyl and ethyl derivatives were prepared in a precisely similar fashion.

The other derivatives of 3-4 dihydroxyphenylethylamine to be considered, are mostly prepared by the same method as that used for preparing the ketone adrenalone and adrenaline itself. In that method, which has been already described, the methylamine used in the last stage of the synthesis of adrenalone may be replaced by other amines or by ammonia. In this way Dakin[2] and Stolz[2] obtained the ketone—



$$\overset{HO}{HO}\!\left\langle\quad\right\rangle\!-CO-CH_2-NH_2$$

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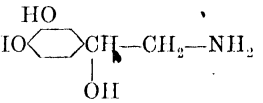
[1] Pyman, *J. C. S.*, 97 (1910), 264.

[2] *Loc. cit.*

and its reduction product—



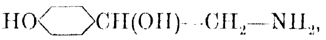
and also the substituted ketones of the type—

$$(HO)_2C_6H_3 \,.\, CO \,.\, CH_2 \,.\, NR_1R_2.$$

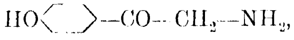
Before considering the physiological action of these substances with two phenolic hydroxyl groups, attention must be given to those synthetic products containing one phenolic hydroxyl group in the para position (*i.e.* those related to tyramine). Most of the compounds of this type resemble tyramine in being derivatives of phenylethylamine, $C_6H_5—CH_2—CH_2—NH_2$, rather than of phenylethanolamine,

$$C_6H_5—CH(OH)—CH_2—NH_2,$$

but one member of the latter class, and also the corresponding ketone, have been prepared and physiologically examined. These are p.-hydroxyphenylethanolamine—

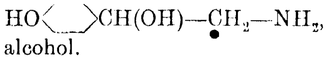


and p.-hydroxy-ω-amino-acetophenone—



which could not be prepared by the method employed in the adrenaline series by using phenol instead of catechol, but which have been prepared instead by the following synthesis[1] (see next page).

p.-Hydroxy-ω-chloro-acetophenone could not be condensed with ammonia, but its acetate could be condensed with potassium phthalimide, and the resultant compound, on removal of the phthalic acid by hydrolysis, yields the desired compound.

The ketone then gives the corresponding secondary alcohol  by reduction with sodium and alcohol.

The other compounds of this series which have been physiologically examined differ from tyramine only in having one or more of the hydrogen atoms of the amine group replaced by alkyl groups.

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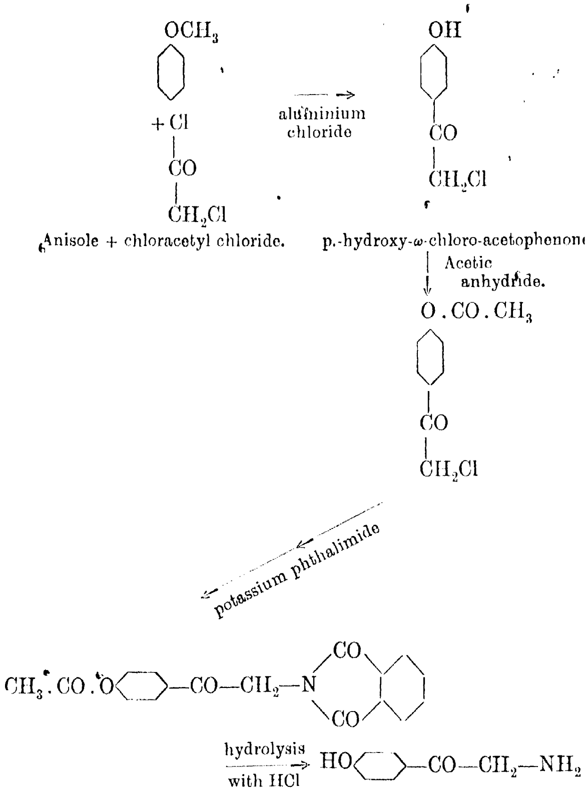
[1] Tutin, Caton, and Hann, *J. C. S.*, 95 (1909), 2113.



Of these, *hordenine*, $HO\langle\ \rangle CH_2-CH_2-N(CH_3)_2$, is a lkaloid, first obtained from barley germs,[1] but it cannot b btained from tyramine by methylation, as on attempting to d his, no compound but the completely methylated quaternar ubstance, hordenine-methiodide—

$$HO.C_6H_4.CH_2-CH_2.N(CH_3)_3I,$$

ould be isolated.[2] *A fortiori* this method of direct methylatio s inapplicable to the preparation of p.-hydroxyphenylethyl methylamine, HO . C_6H_4 . CH_2—CH_2—NH . CH_3. Both these compounds have, however, been prepared by synthetic methods The synthesis of hordenine was first accomplished according to the following scheme, which is self-explanatory :—[1]

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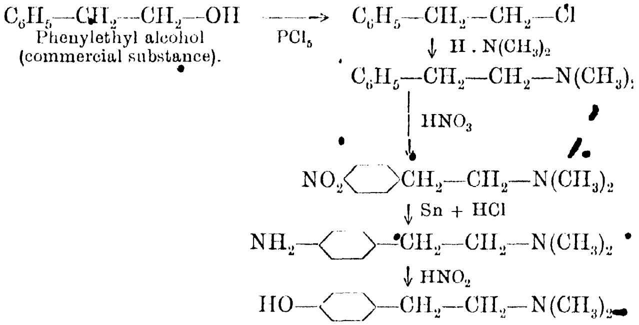
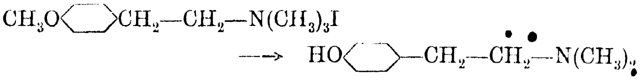
[1] Léger, *C. R.*, **142** (1906), 108; **143**, 234, 916.
[2] Barger, *J. C. S.*, **95** (1909), 2193.

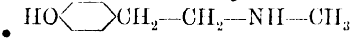


Very shortly afterwards, Rosenmund[2] obtained hordenine by the direct methylation of p.-methoxyphenylethylamine with alcoholic potash and methyl iodide, and separation of the primary, secondary, tertiary, and quaternary compounds thus obtained. The methoxy group is then converted into hydroxyl with hydriodic acid. Hordenine was also obtained by this investigator by the action of hydriodic acid on p.-methoxyphenyl-trimethylammonium iodide—

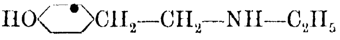


Hordenine is manufactured by the methylation of p.-hydroxyphenylethylamine with methyl chloride (CH_3Cl).

The p.-hydroxyphenylethylmethylamine—



and p.-hydroxyphenylethylethylamine—



were prepared by the methylation and ethylation respectively of the acetyl or benzene-sulphonyl derivatives of p.-methoxyphenylethylamine, the former by both methods, the latter only by means of the benzene-sulphonyl derivatives.[1] p.-Methoxyphenylethylamine is prepared as indicated on pages 140-141, and the rest of the synthesis is easily understood from the accompanying scheme:—

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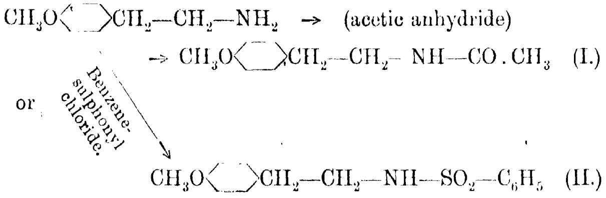
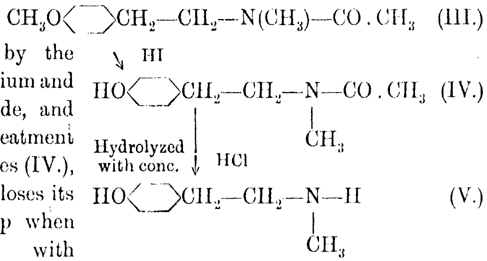
[1] Barger, *J. C. S.*, 95 (1909), 2193.

[2] Rosenmund, *Ber.*, 43 (1910), 306.



In the case of the acetyl derivative (I.), the substance (III.)— is formed by the action of sodium and methyl iodide, and this on treatment with HI gives (IV.), which then loses its acetyl group when hydrolyzed with concentrated HCl in sealed tubes. The benzene-sulphonyl derivative is treated in a similar manner, and the corresponding ethyl-amine is obtained by using ethyl iodide instead of methyl iodide.



The Physiological Action of these Compounds.—The relation between the chemical structure and the physiological (sympathomimetic) action of amines has formed the subject of an extended investigation by Barger and Dale.[2] Dakin[3] and Loewi and Meyer[4] had examined many of the ketones of the general formula $(HO)_2C_6H_3—CO—CH_2—NR_1R_2$, and the corresponding secondary alcohols of the type—

$$(HO)_2C_6H_3—CH(OH)—CH_2—NR_1R_2$$

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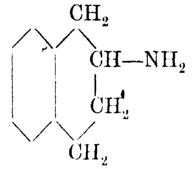
[1] Walpole, *J. C. S.*, **97** (1910), 941.
[2] Barger and Dale, *Journ. of Physiol.*, **41** (1910), 19-59.
[3] Dakin, *Proc. Roy. Soc.*, **76 B** (1905), 498.
[4] Loewi and Meyer, *A. e. P. P.*, **53** (1905), 213.

and they found that in most cases, as for example with adrenaline itself, reduction to the secondary alcohol greatly increased the adrenaline-like action, but where R_1 and R_2 represent relatively complex radicles, Dakin found no such increase of activity on reduction. The physiological effects examined by Barger and Dale were not confined to rise of blood pressure, but included dilatation of the pupil, action on the cat's uterus, etc., for the details of which the original paper should be consulted. Besides the various compounds that have been described in the preceding sections of this chapter, various other amines were examined.

Of the various aliphatic amines that were investigated, the only ones which were found to produce a marked rise of blood pressure were the higher open-chain primary amines, such as amylamine, $C_5H_{11} . NH_2$, and hexylamine, $C_6H_{13} . NH_2$. Of these, the normal compounds with unbranched side chains were found to be more active than the corresponding *iso* compounds with branched side chains. Trimethylamine, $N(CH_3)_3$, has practically no pressor action, and neither has tetraethylammonium iodide, $N(C_2H_5)_4I$. Cadaverine, $NH_2 . [CH_2]_5 . NH_2$ the only diamine examined, was found to have the opposite action (depressor instead of pressor).

A large number of *fatty-aromatic amines without a phenolic hydroxyl group* were also investigated, and it was found that marked sympathomimetic action was associated only with those containing an amino group attached to the second carbon atom of the side chain. β-phenyl-ethylamine, $C_6H_5—CH_2—CH_2—NH_2$ for example, produces all the characteristic sympathomimetic effects. In the series containing two phenolic hydroxyl groups in the 3-4 position, the introduction of an aliphatic hydroxy in the β-position of the side chain, and the methylation of the amino group have an important effect in intensifying the action but in the present series, this does not hold, methyl-phenylethylamine, $C_6H_5—CH_2—CH_2—NH . CH_3$, phenylethanolamine $C_6H_5—CH(OH)—CH_2—NH_2$, and methyl-phenylethanolamine $C_6H_5—CH(OH)—CH_2—NH . CH_3$, differing but little in their action from phenylethylamine itself. *Ac.*-tetrahydro-β-naphthylamine—



which may be regarded as a derivative of this type, is more active than phenylethylamine in producing a rise of blood-pressure, but is less active than p.-hydroxyphenylethylamine (tyramine), the simplest member of the next series, namely:—

Amines with one Phenolic Hydroxyl Group.—The sources and preparation of many of these have already been mentioned. Methylation of the amino group produces very little increase in the activity, $HO—C_6H_4—CH_2—CH_2—NH . CH_3$ (see page 145), being only very slightly more active than the primary amine, while the ethyl derivative—

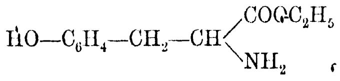
$$HO—C_6H_4—CH_2—CH_2—NH—C_2H_5$$

is less active than either the methyl derivative or the parent substance. The tertiary base, $HO—C_6H_4—CH_2—CH_2—N(CH_3)_2$, which is the alkaloid hordenine, has a relatively very weak action, but the quaternary base, hordenine methiodide, $HO—C_6H_4—CH_2—CH_2—N(CH_3)_3I$, although it has no sympathomimetic action, is of interest as it is one of the few exceptions to the rule of Crum Brown and Fraser that quaternary bases have a curare-like action. Instead, its action resembles that of nicotine, which is a physiological antagonist of curare.

Destruction of the basic property is accompanied by loss of activity, acetyl-p.-hydroxyphenylethylamine—

$$HO—C_6H_4—CH_2—CH_2—NH . CO . CH_3,$$

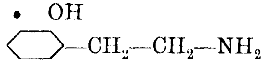
for example, being inactive. Tyrosine ethyl ester—



$$HO—C_6H_4—CH_2—CH\begin{matrix}\diagup COOC_2H_5\\ \diagdown NH_2\end{matrix}$$

lso inactive. A phenolic hydroxyl group in the 3 position is s active as in the 4 position, the meta-hydroxy compound, $_2$—CH_2—NH_2, closely resembling the corresponding para-derivative (tyramine), but in the 2 position it has no effect

ortho - hydroxyphenylethylamine,



being no more active than phenylethylamine itself.

Amines with two Phenolic Hydroxyl Compounds.—Th following compounds in which the two hydroxyl groups are i the 3-4 position were tested :—

(a) *Derivatives of aceto-catechol (ketones).*

(1) Amino-aceto-catechol, $(HO)_2C_6H_3$—CO—CH_2—NH_2.
(2) Methylamino-aceto-catechol—
$(HO)_2C_6H_3$—CO—CH_2—NH—CH_3.
(3) Ethylamino-aceto-catechol—
$(HO)_2C_6H_3$—CO—CH_2—NH—C_2H_5.
(4) Propylamino-aceto-catechol—
$(HO)_2C_6H_3$—CO . CH_2—NH—C_5H_7.
(5) Trimethylamino-aceto-catechol chloride—
$(HO)_2C_6H_3$—CO—CH_2—$N(CH_3)_3Cl$.

(b) *Derivatives of ethyl-catechol.*

(6) Amino-ethyl-catechol, $(HO)_2C_6H_3$—CH_2—CH_2—NH_2.
(7) Methylamino-ethyl-catechol—
$(HO)_2C_6H_3$—CH_2—CH_2—NH—CH_3
(8) Ethylamino-ethyl-catechol—
$(HO)_2C_6H_3$—CH_2—CH_2 —NH—C_2H_5.
(9) Propylamino-ethyl-catechol—
$(HO)_2C_6H_3$—CH_2—CH_2—NH—C_3H_7.
(10) Trimethylamino-ethyl-catechol chloride—
$(HO)_2C_6H_3$—CH_2—CH_2—$N(CH_3)_3Cl$.

(c) *Derivatives of ethanol-catechol (secondary alcohols).*

(11) Amino-ethanol-catechol—
$(HO)_2C_6H_3CH(OH)$—CH_2—NH_2.
(12) Methylamino-ethanol-catechol (adrenaline)—
$(HO)_2C_6H_3$—CH(OH)—CH_2—NH—CH_3.

And also—

(13) 2-4 dihydroxy-ω-amino-acetophenone[1]—

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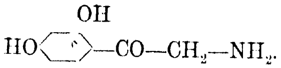
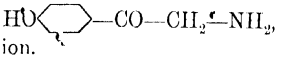
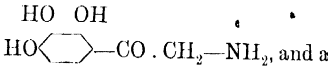
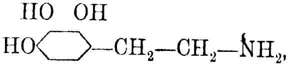
[1] Tutin, *J. C. S.*, 97 (1910), 2495-2524.


$(HO)_2C_6H_3—CO—CH_2—NH_2$.

It was found that catechol itself has no sympathomimetic action, although it produces a rise of blood-pressure. The following table shows the comparative strength of the action of the various amines in causing a rise of blood-pressure :—

Substance (numbered as before).	Ratio of activity.
(1) $(HO)_2C_6H_3—CO—CH_2—NH_2$	1·5
(2) $(HO)_2C_6H_3—CO—CH_2—NH—CH_3$	
(3) $(HO)_2C_6H_3—CO—CH_2—NH—C_2H_5$	2·25
(4) $(HO)_2C_6H_3—CO—CH_2—NH—C_3H_7$	0·25
(6) $(HO)_2C_6H_3—CH_2—CH_2—NH_2$	1·0
(7) $(HO)_2C_6H_3—CH_2—CH_2—NH—CH_3$	5·0
(8) $(HO)_2C_6H_3—CH_2—CH_2—NH—C_2H_5$	1·5
(9) $(HO)_2C_6H_3—CH_2—CH_2—NH—C_3H_7$	0·25
(11) r- $(HO)_2C_6H_3—CH(OH)—CH_2—NH_2$	50
(12) r- $(HO)_2C_6H_3—CH(OH)—CH_2—NH—CH_3$ (r-adrenaline) . .	35

The ratios shown are only approximate, and vary to some extent with the sensitiveness of the animal. The compound numbered (7), which was obtained from an isoquinoline derivative, causes a more prolonged rise of blood-pressure than adrenaline. The quaternary bases numbered (5) and (10) resemble hordenine-methiodide in having a nicotine-like action. This is less than that of hordenine-methiodide in the case of (5), and greater in the case of (10). Although these bases produce a rise of blood-pressure, they are not included in the above table, as their action is not truly sympathomimetic, as is evidenced by their action on other organs. The substance numbered (13) on the list, having the hydroxyl groups in the 2-4 position, is no more active than the corresponding compound  $HOC_6H_4—CO—CH_2—NH_2$, having one hydroxyl in the 4 position.

Further evidence of the non-significance of a hydroxyl group in the 2 position is shown by the trihydroxy compounds, amino-aceto-pyrogallol,  $(HO)_3C_6H_2—CO.CH_2—NH_2$, and amino-ethyl-pyrogallol,  $(HO)_3C_6H_2—CH_2—CH_2—NH_2$, which, although more susceptible to oxidation than the 3-4-dihydroxy comounds, show no increased sympathomimetic action in comarison with the latter.

The main conclusions are summed up by these investigators s follows :—

"(1) An action simulating that of the true sympathetic ervous system is not peculiar to adrenine, but is possessed y a large series of amines, the simplest being primary fatty mines. We describe all such amines and their action as sympathomimetic.'

"(2) Approximation to adrenine in structure is, on the whole, attended with increasing intensity of sympathomimetic ctivity, and with increasing specificity of the action.

"(3) All the substances producing this action in characterstic manner are primary and secondary amines. The quaernary amines corresponding to the aromatic members of the eries have an action closely similar to that of nicotine.

"(4) The optimum carbon skeleton for sympathomimetic ctivity consists of a benzene ring with a side chain of two arbon atoms, the terminal one bearing the amino group. Another optimum condition is the presence of two phenolic hydroxyls in the 3-4 position relative to the side chain; when hese are present, an alcoholic hydroxyl still further intensifies he activity. A phenolic hydroxyl in the 2 position does not ncrease the activity.

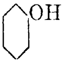
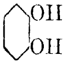
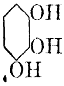
"(5) Catechol has no sympathomimetic action.

"(6) Motor and inhibitor sympathomimetic activity vary to some extent independently. Of the catechol bases those with a methylamino group, including adrenine, reproduce inhibitor sympathetic effects more powerfully than motor effects: the opposite is true of the primary amines of the same series.

"(7) Instability and activity show no parallelism in the series."

CHAPTER X.

DERIVATIVES OF PHENOL (ANTISEPTICS).

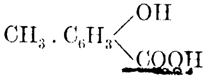
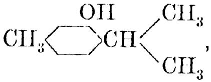
THE entrance of a hydroxyl group into the benzene nucleus increases its solubility and its reactivity, and, as might be expected, these changes are accompanied by an increase in its physiological activity and its antiseptic powers. Phenol, C_6H_5OH, was the first antiseptic to be widely used, and its antiseptic powers are increased by the entrance of halogen or additional hydroxyl groups into the nucleus. The entrance of more hydroxyl groups adjacent to the first, also increases the toxicity of the substance, phenol, , being less toxic than catechol, , and this in its turn being less toxic than pyrogallol, .

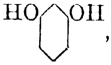
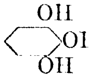
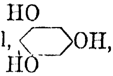
On the other hand, the entrance of alkyl groups into the nucleus lowers the toxicity and increases the antiseptic properties, and for this reason the three isomeric *cresols*, $C_6H_4(OH)(CH_3)$, are better antiseptics than phenol. Unfortunately this advantage is marred by the fact that they are much less soluble in water than phenol, and hence many attempts have been made to obtain derivatives of cresol which should retain their antiseptic properties, and yet be more soluble in water.

The cresols form an emulsion with (hard) yellow soap, and an emulsion of this sort is known as *Creolin*, but it suffers from the drawback that it is demulsified by mineral acids, alkalies, or common salt. A solution of the cresols in soft soap is known as *Lysol*, and has attained wide use as an antiseptic. It is prepared by mixing the crude coal-tar cresol (cresylic acid) with linseed oil in presence of alcohol until completely saponified, and the final product dissolves easily in water.[1]

Lysol solutions suffer from the drawback that they vary in their antiseptic power according to the amount of cresol present, and hence they have to be tested bacteriologically, but they possess the advantage of being less poisonous than phenol or mercuric chloride.

The cresols can also be rendered soluble in water by mixing them with the sodium salts of organic sulphonic acids. Thus the cresols and other insoluble substances can be brought into solution by mixing them with the neutralized products obtained from the action of sulphuric acid on resinous oils, etc.

The sodium salts of cresotinic acid,  $CH_3 . C_6H_3 < \begin{matrix} OH \\ COOH \end{matrix}$, salicylic acid, and of various fatty acids, can also be used to render the cresols soluble. The only substances of this type which are of practical importance are solutions of cresol in soap, but a solution of cresol in sodium cresotinate has been sometimes used internally under the name of *Solveol*, as a substitute for guaiacol and creosote. Thymol,  $CH_3 \langle \, \rangle CH < \begin{matrix} CH_3 \\ CH_3 \end{matrix}$ (OH), is used as an antiseptic and anthelminthic,[2] but for the latter purpose thymol carbonate has been recommended instead. It is prepared from thymol by the action of carbonyl chloride, $COCl_2$, and is called *Thymatol*.

The polyhydric phenols have not been much used in therapeutics. Resorcinol, , has, however, found considerable application in dermatology, and its acetyl derivative, $C_6H_4(OH)(O . CO . CH_3)$, is used in the same way under the name of *Euresol*. Pyrogallol, , is also used in some skin diseases on account of its reducing properties. The high price of phloroglucinol, , has prevented it from coming into therapeutic use.

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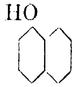
[1] D. R. P., 52,129.

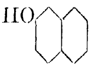
[2] Anthelminthic is a term denoting a substance used as a poison for

A mixture of various phenyl-sulphuric acids, known as *Aseptol*, is obtained by allowing cold fuming sulphuric acid to act on phenol, and adding alcohol to the reaction product. The substance thus obtained is unstable and liberates phenol, but has no special value.

The naphthols are not much used in therapeutics; α-naphthol

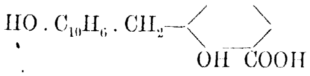


α-naphthol.



β-naphthol.

is more poisonous than β-naphthol, and so only the latter finds any therapeutic application. Its sodium salt is soluble in water, and has received the name *Microcidin*. A better-known derivative is *Epicarin*—



a non-corrosive antiseptic which is strongly acid and forms soluble salts. It is said to be useful in skin diseases, such as scabies.

An extended investigation on the effect of substituting halogen atoms or alkyl groups for hydrogen in the nucleus of phenol, and on the germicidal power of other phenolic derivatives, has been carried out by Bechhold and Ehrlich.[1] The antiseptic power of these compounds was compared by finding the amount of the phenol required to prevent the growth of certain bacteria under standard conditions, the diphtheria bacillus being the one usually chosen. It was found that the entrance of chlorine or bromine into the nucleus of phenol is accompanied by an increase in the antiseptic power. Trichlor-phenol was found to be twenty-five times and tri-brom-phenol forty-six times as active as phenol itself. Tetrachlor-, pentachlor-, and pentabrom-phenols were increasingly active in the order given, the last-named being five-hundred times as powerful in its action as phenol itself. In the early part of this chapter it was stated that the entrance of alkyl groups into the nucleus of phenol (as in the cresols) increases the antiseptic power, and this was found to be the case with the halogen derivatives of the phenols also. The tetrabrom derivatives of all three cresols were found to be far more active in their germicidal properties than tetrachlor- or tetrabrom-phenol, the derivative of ortho-cresol being slightly more powerful than the meta or para isomerides. A one-per-cent. solution of this substance takes less than two minutes to kill the diphtheria bacillus, whereas a corresponding solution of phenol requires more than ten. As the toxicity of this compound is stated to be comparatively slight, it might find useful application, but the toxicity is apparently still too great to permit of its being used internally.

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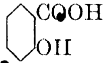
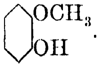
[1] *Zeit. physiol. Chem.*, 47 (1906), 173.

In fact, although it was found that the entrance of a ~~bromine~~ atom reduces the toxicity and characteristic convulsive action of phenol itself, nevertheless the conclusion was arrived at that none of these compounds were suitable for use as internal disinfectants, as they were no more damaging to bacteria than to the animal body. The further introduction of halogen is accompanied by a rise of toxicity, that of the tribrom- and trichlor-phenols being about equal to that of phenol itself, while the tetra- and penta-halogen derivatives are extremely toxic.

The simple phenolic compounds and their halogen derivatives are therefore not suitable for internal disinfection, but greater success has attended the use of phenolic derivatives containing a second group in the molecule, which lowers the toxicity of the compound.

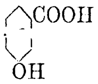
The introduction of a carboxyl group, as is usually the case, lowers the toxicity. It is true that it greatly lowers the antiseptic power of phenol, but in spite of this, the ortho-carboxylic acid of phenol, 

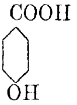
(salicylic acid), has marked antiseptic properties, and it has proved to be of great value medicinally.

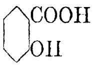
Another type of phenolic derivatives which has proved of value as an internal antiseptic, is represented by guaiacol, 

. Salicylic acid and its derivatives are used more on account of their value in lowering the temperature and diminishing the pain in rheumatism rather than for the sake of their antiseptic properties, but the acid and its ester with phenol (salol) are also used as antiseptics. The derivatives of salicylic acid will be discussed in the next section, and those of guaiacol in the one after that.

Salicylic Acid and Salols.—As has been so frequently pointed out, the introduction of a carboxyl group into phenol lowers its physiological activity. Meta-hydroxy- and para-hydroxy-benzoic acids are practically inert physiologically, but *salicylic acid*, in addition to having a very slight toxicity, possesses special therapeutic properties which are of very great value.


m.-hydroxy-benzoic acid.


p.-hydroxy-benzoic acid.

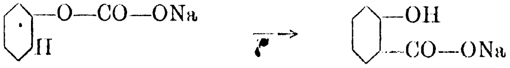

Salicylic acid.

The most important of these is a powerful action against most of the symptoms of acute rheumatism, which is marvellous in its intensity. Salicylic acid also possesses marked antiseptic properties, for which it is often used to check gastric fermentation, as its irritant action on the stomach is much less than that of phenol, and for the same reason it is often used to prevent putrefaction in milk, beer, etc. In the body it is rapidly absorbed, and circulates as the sodium salt, which is often used therapeutically instead of the free acid, as of course its action is the same, and it has the advantage of being far more soluble in water.

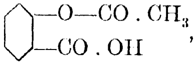
Salicylic acid was first synthesized by Kolbe[1] by the action of carbon dioxide on phenol. Originally this was carried out by passing carbon dioxide into hot phenol in the presence of sodium, but it was found better for technical purposes to prepare dry sodium phenate, C_6H_5ONa, and to pass carbon dioxide into this. Even by this method, however, only a 50-per-cent yield of salicylic acid was obtained, and if potash were used instead of soda, para-hydroxybenzoic acid was the

[1] *Annalen*, **113** (1860), 115; **125** (1865), 201; D. R. P., 426.

chief product. This process was greatly improved by Schmitt,[1] who heated sodium phenyl carbonate—



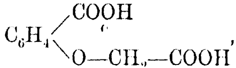
under pressure at 140° C., by which means a quantitative yield of sodium salicylate was obtained. This process is also applicable to the preparation of naphthol-carboxylic acid and oxyquinoline-carboxylic acid.[2]

Salicylic acid and its sodium salt frequently produce unpleasant gastric symptoms, and to overcome this defect various derivatives have been prepared, one of which, acetyl-salicylic acid, , is of very great importance. This substance is known under various trade names, such as *Aspirin*, etc.

It has the characteristic action of salicylic acid, being hydrolyzed in the intestine with liberation of sodium salicylate, and it also has a slight sedative action of its own. It is a favourite remedy for feverish colds, headaches, etc.

It was first obtained by heating salicylic acid with excess of acetic anhydride or acetyl chloride, but a better yield is obtained by carrying out the acetylation in the presence of a condensing agent, such as sulphuric acid, zinc chloride, or sodium acetate. Propionyl, butyryl, and other acyl derivatives of salicylic acid have been obtained in the same way.

Of these, methylenecitrylsalicylic acid is known as *Novaspirin*, salicylosalicylic acid as *Diplosal*, and succinylsalicylic acid as *Diaspirin*. The calcium salt of acetylsalicylic acid is known as *Soluble Aspirin* or *Kalmopyrin*, and the sodium salt as *Tylnatrin*. These, and also the lithium salt, *Hydropyrin*, are more soluble in water than is Aspirin itself, which they resemble in their therapeutic effect, whilst the last named has also the characteristic action of lithium salts (*cf.* p. 220).

A substance which is isomeric with aspirin has been obtained by the action of acetyl chloride on salicylic acid in presence of ferric chloride. It is an aceto-salicylic acid of the formula $(CH_3 . CO) . C_6H_3 . (OH)(COOH)$, and is not toxic, but it has far less antiseptic power than salicylic acid itself. Salicylacetic acid,  $C_6H_4\langle{}^{COOH}_{O—CH_2—COOH}$, in which the hydroxylic hydrogen is replaced by an acetic-acid residue, (—CH_2—COOH), instead of by the acetyl group, (CO . CH_3), was first obtained by the oxidation of the ortho-aldehyde of hydroxyphenyl-acetic acid.[1] Subsequently, improved methods of preparing it were devised,[2] but this substance does not appear to have come into use as a drug.

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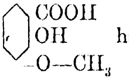
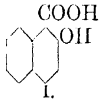
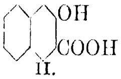
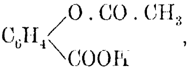
[1] D. R. P., 29,939.

[2] *Ibid.*, 31,240.

Schmitt's modification of Kolbe's salicylic acid synthesis has been extended to several other substances. For example,  has been prepared from guaiacol, but it has not found its way into therapeutics, and from α- and β-naphthols the corresponding carboxylic acids have been obtained, in each of which the carboxyl group is in the ortho position to the hydroxyl group. The acid (I.) thus obtained from β-naphthol is very unstable, splitting up into naphthol and carbon dioxide, but if the temperature at which the synthesis is carried out be raised to 200°-250° C., a stable acid (II.) is obtained.


I.


II.

Of the various derivatives of salicylic acid that have been mentioned, acetyl-salicylic acid,  $C_6H_4\langle{}^{O . CO . CH_3}_{COOH}$, is the only one of real practical value, but other substances have been used instead of salicylic acid itself, chiefly on account of the distrust with which synthetic salicylic acid was at one time viewed. This distrust arose from the fact that the synthetic acid used often to contain the therapeutically useless para-hydroxybenzoic acid, as well as sometimes being contaminated with the positively harmful cresols. To make sure of obtaining a natural product, some physicians preferred to prescribe the glucoside

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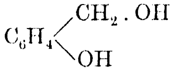
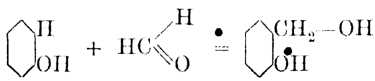
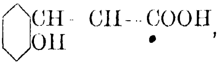
[1] *Ber.*, 17 (1884), 2995. [2] D. R. P., 93,110, 110,370.

salicin instead of salicylic acid itself. This glucoside is hydrolyzed by the organism, with liberation of *saligenin* (salicyl alcohol),  $C_6H_4\begin{cases}CH_2 . OH \\ OH\end{cases}$, which then forms salicylic acid by slow oxidation. In this way, the use of saligenin or salicin ensures a gradual action of the salicylic acid. Saligenin may be synthesized by the action of formaldehyde on phenol—



Ortho-coumaric acid,  bears the same relationship to cinnamic acid, $C_6H_5—CH=CH . COOH$, as salicylic acid does to benzoic acid, and as cinnamic acid is more physiologically active than benzoic acid, it was to be expected that *o*-coumaric acid would have even more powerful antiseptic properties than salicylic acid. This was found to be the case, all three coumaric acids having a marked germicidal action, which is strongest in the case of the ortho acid.

Incidentally, it should be noted that *sodium cinnamate* has been found to be active in promoting leucocytosis, and has been recommended in cases of tuberculosis. Its esters with guaiacol, phenol, ortho and para-cresol are too irritant to be of use, but its meta-cresol ester is free from these drawbacks, and is used under the name of *Hetocresol* as a dusting powder for tuberculous wounds. A similar compound of cinnamic acid with thymol has also been prepared.[1]

A dilute aqueous solution of sodium cinnamate has been used in Germany under the name *Hetol*, and a glycerol solution of this substance which has certain advantages over the aqueous one was advocated by Morgan in 1902. The use of drugs, such as sodium cinnamate and sodium ortho-coumarate, which produce leucocytosis,[2] appears to have given promising results in the treatment of inoperable cancer when combined with local treatment with substances such as copper oleate and antimony oxide.[1]

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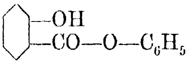
[1] D. R. P., 99,567, 107,230.

[2] Leucocytosis denotes an increase in the count of the white blood-corpuscles.

The acetyl derivative of *o*-coumaric acid which is suitable for being taken by the mouth has been introduced by Martindale under the name of *Tylmarin*.

Salol and Esters of a Similar Type.—The first ester, both the components of which are physiologically active, to be used in medicine was *salol*,  (phenyl salicylate). The introduction of this substance by Nencki marked an important development in pharmacology, and many other attempts have been made to convert substances which are too toxic for ordinary use into esters from which the active component is liberated so slowly that it produces no injurious by-effects. In the case of salol itself the ester on hydrolysis in the intestine liberates phenol and salicylic acid, the hydrolysis taking place so gradually that the former component can exert its antiseptic effect without, under ordinary conditions, giving rise to its characteristic toxic symptoms. In this case both components of the ester are active, but this "salol principle," as it is called, can be extended to esters in which only the acid or the alcohol is active, but the use of which in the free state is hindered owing to the possession of toxic or corrosive properties.

Derivatives of this kind may be classed as "partial salols," and comprise two types :—

(1) Esters in which an active (aromatic) acid is esterified with an inert hydroxylic substance (alcohol), and which therefore bear a general resemblance in their physiological action to the acid from which they are derived, but which may differ from it in being free from harmful by-effects.

(2) Esters in which an active hydroxyl compound (alcohol or phenol) is esterified by an inactive acid. In this case the action of the substance resembles that of the alcohol or phenol, the sodium salt of the acid being inert.

It must not be lost sight of, however, that the ester itself may exert a specific action in the unhydrolyzed state (*e.g.*

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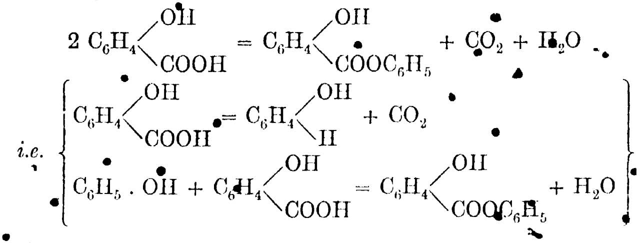
[1] H. Lovell Drage, *Lancet*, 7th November, 1908, p. 1367.

triacetin: see Chap. II., p. 22), and therefore in every case the physiological action of the ester must be experimentally demonstrated before it can be used in therapeutics, as *a priori* reasoning based on the behaviour of the component acid and alcohol might be upset by the specific action of the ester.

Dealing first with the true salols themselves, it may be said with confidence that no other ester of this class is nearly as important as salol itself. It was found by Nencki that fatty or aromatic acids when allowed to react with phenols in presence of zinc chloride, aluminium chloride, etc., yielded ketones, but if $POCl_3$ were employed as the condensing agent, esters were formed. Thus salol itself, $C_6H_4{<}\begin{smallmatrix}OH\\ CO.O.C_6H_5\end{smallmatrix}$, is produced by heating two molecules of phenol, two molecules of salicylic acid and one of $POCl_3$ at 120° C.[1] This method has also been applied to the preparation of the esters of salicylic acid with many other phenols, naphthols, resorcin, etc., and also to the preparation of the esters of other acids, such as nitro-salicylic and oxynaphthoic. A cheaper and simpler modification of this method of preparation is to allow carbonyl chloride to react with an equi-molecular mixture of the sodium salts of the phenol and of the acid. The ester thus formed can usually be separated from the reaction mixture by distilling it off with steam. In this way an enormous number of esters of a similar type to salol have been prepared.[2]

Salol is also obtained by heating salicylic acid alone at 160°-240° C., provided that the water split off by the reaction be removed by distillation, and that the access of air be prevented.[3]



$$2\,C_6H_4{<}\begin{smallmatrix}OH\\ COOH\end{smallmatrix} = C_6H_4{<}\begin{smallmatrix}OH\\ COOC_6H_5\end{smallmatrix} + CO_2 + H_2O$$

$$i.e.\left\{\begin{array}{l} C_6H_4{<}\begin{smallmatrix}OH\\ COOH\end{smallmatrix} = C_6H_4{<}\begin{smallmatrix}OH\\ H\end{smallmatrix} + CO_2 \\ C_6H_5\,.\,OH + C_6H_4{<}\begin{smallmatrix}OH\\ COOH\end{smallmatrix} = C_6H_4{<}\begin{smallmatrix}OH\\ COOC_6H_5\end{smallmatrix} + H_2O \end{array}\right\}$$

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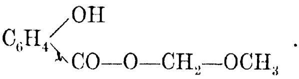
[1] D. R. P., 38,973, 39,184, 43,173.

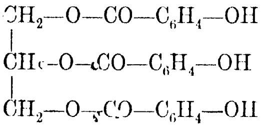
[2] *Ibid.*, 46,756, 57,941, 68,111, 70,487; and also Nencki, C. R., **108** (1889), 254.

[3] D. R. P. 62,275.

Another method for the preparation of salol is by heating polysalicylide $(C_7H_4O_2)x$ (obtained by heating salicylic acid with $POCl_3$, see Chap. IV.) alone with phenol.[1]

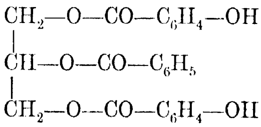
The higher members of the salol series may be prepared by heating salol itself with the higher phenol, whereby the lower phenol is replaced by the higher. This method is especially suitable for use with phenols which are too reactive to be treated with the vigorous condensing agents used in the first methods; *e.g.* hydroquinone, eugenol, carvacrol, etc.[2]

"Partial Salols" of the First Type.—*Methyl salicylate* (*oil of wintergreen*) is the best known of these. The synthetic product is superior to the natural in being free from the irritant effects of the latter. It is slower in its action than salicylic acid itself. Ethyl salicylate appears to have a specific action of its own, and produces undesirable effects, and hence is not used in therapeutics. *Mesotan* or *Ericin* is the methoxy-methyl ester of salicylic acid,  $C_6H_4\begin{cases} OH \\ CO—O—CH_2—OCH_3 \end{cases}$. Many esters of glycerol with salicylic acid, benzoic acid, p.-cresotinic acid, and anisic acid have been prepared, such as—



$$\begin{array}{l} CH_2—O—CO—C_6H_4—OH \\ | \\ CH—O—CO—C_6H_4—OH \\ | \\ CH_2—O—CO—C_6H_4—OH \end{array}$$

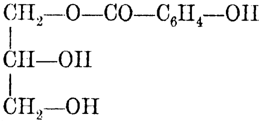
Trisalicylin.



$$\begin{array}{l} CH_2—O—CO—C_6H_4—OH \\ | \\ CH—O—CO—C_6H_5 \\ | \\ CH_2—O—CO—C_6H_4—OH \end{array}$$

Disalicylbenzoin.

and



$$\begin{array}{l} CH_2—O—CO—C_6H_4—OH \\ | \\ CH—OH \\ | \\ CH_2—OH \end{array}$$

Monosalicylin.

The last named is used under the name of *Glycosal*.[3]

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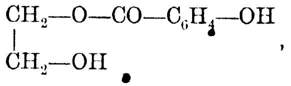
[1] F. R. P., 73,452.

[2] *Ibid.*, 111,656.

[3] *Ibid.*, 58,396, 126,311, 127,139.

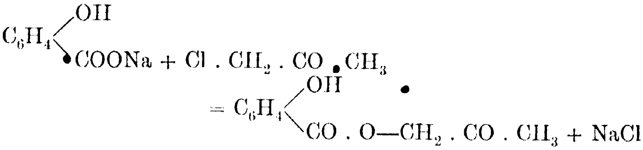
The monoglycol ester of salicylic acid,



$$\begin{array}{l}CH_2—O—CO—C_6H_4—OH \\ | \\ CH_2—OH\end{array},$$

is known as *Spirosal.*

Salacetol is obtained by the action of monochloracetone on sodium salicylate—

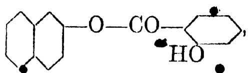


$$C_6H_4\begin{cases}OH \\ COONa\end{cases} + Cl . CH_2 . CO . CH_3 = C_6H_4\begin{cases}OH \\ CO . O—CH_2 . CO . CH_3\end{cases} + NaCl$$

and is therefore the salicylic ester of acetol, $HO—CH_2—CO—CH_3$. It is rapidly saponified in the intestine, but has no particular advantage over salicylic acid.[1]

The methyl esters of the acyl salicylic acids have also been used medicinally. Methyl acetylsalicylate is known as *Methylrhodin*, and methyl benzoylsalicylate as *Benzosalin.*

"Partial Salols" of the Second Type, in which only the phenol is the active part, comprise carbonates and esters of fatty acids. Of these, the esters of guaiacol and creosote are of special importance, and will be considered in the next section of this chapter (which deals with creosote and guaiacol derivatives), together with the general methods of their preparation. Thymol carbonate is known as *Thymatol.*

True Salols.—Of esters of the type of salol in which both components are active, salol itself is the most important, and next to it comes β-naphthol salicylate, , which is known as *Betol*, and as *Naphtholsalol.* The benzoate of β-naphthol is also used to a considerable extent under the name of *Benzonaphthol.* Menthyl salicylate is used medicinally under the names of *Salimenthol* and *Salit.* In addition to the esters of salicylic acid itself, the phenyl esters of acetylsalicylic and of salicylosalicylic acid are used, and are known respectively as *Vesipyrin* and *Disalol.*

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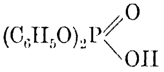
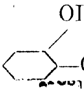
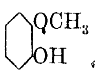
[1] D. R. P., 70,054.

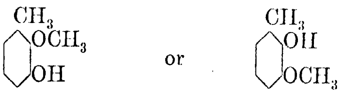
In general it is only the monobasic acids which lend themselves in an economical manner for use as salols, as the esters of polybasic acids usually only split off one molecule of the phenol, the rest being excreted still in combination with the acid. Thus, for example, triphenyl phosphate, $(C_6H_5O)_3PO$, is hydrolyzed in the intestine into diphenyl-phosphoric acid,  $(C_6H_5O)_2P\begin{smallmatrix}\nearrow O\\ \searrow OH\end{smallmatrix}$, and phenol, C_6H_5OH, the former not being further decomposed in the organism, and thus only a third of the phenol is utilized.

Another type of salicylic acid derivative comprises those in which it is combined with basic radicles. Salicyl-amide, —CO—NH$_2$, is more soluble than salicylic acid, and has a more marked analgesic action. Many compounds have been prepared in which salicylic acid is combined with substances having antipyretic and analgesic properties, especially the derivatives of acetyl-para-amino-phenol. The salicylate of acetyl-para-amino-phenol, HO NH . CO . CH$_3$, is known as *Salophen*.[1] In the same manner lactylamino-phenol can be condensed with salicylic acid.[2]

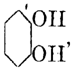
Guaiacol, Creosote, and their Derivatives.—Beechwood tar has long been used in the treatment of phthisis, and the chief active ingredients appear to be guaiacol and creosol.



Guaiacol.



Creosol.

These can be obtained from the beechwood tar, but *guaiacol* is also largely produced by synthetic methods. It can be obtained by the partial methylation of catechol, , but this method is too expensive for technical use, and a cheaper synthesis is that which starts from ortho-anisidine. This substance is prepared from ortho-nitro-phenol by methylation and subsequent reduction. It is then diazotized, and the solution poured into sulphuric acid containing a large quantity of sodium sulphate, heated to 135°-160° C., whereupon the guaiacol distils over with the steam as it is formed. In this way the production of by-products is diminished.

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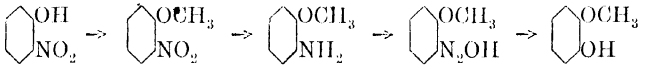
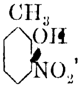
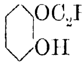
[1] D. R. P., 62,533, 69,789.

[2] *Ibid.*, 82,635. See also Chap. V.



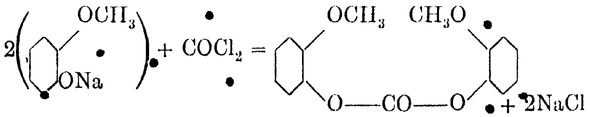
Creosol has been obtained in a similar way from , but the preparation of this compound from ortho-cresol is apparently too expensive for it to be used commercially.

Guaiacol, like phenol, is corrosive and poisonous, and it is probable that creosol would be less toxic, though more strongly antiseptic, in the same way as cresol and phenol.

Guaiathol, , and other higher homologues have been prepared by heating catechol and the required alcohol under pressure with zinc chloride at 160°-220° C., but they are more expensive than guaiacol and have no advantage over it.

With the object of diminishing the unpleasant and toxic properties of guaiacol and creosote, various derivatives have been prepared in which the hydroxyl group is esterified with an acid according to Nencki's salol principle. Carbonic acid was the first used, and various other organic and inorganic acids have also been tried with varying degrees of success. In every case, the action of the compound is due to the guaiacol split off in the intestine.

Guaiacol carbonate, known as *Duotal,* is prepared by the action of phosgene on an alkaline solution of guaiacol.[1]



Duotal is thus obtained as an insoluble preparation, which has less toxicity and unpleasant taste than guaiacol itself, but which is not quite tasteless. In the same way, carbonates of menthol, borneol, carvacrol, thymol, creosol, eugenol, etc., have been prepared, and also the corresponding esters of carbamic acid using chlorocarbonic amide instead of $COCl_2$—[1]

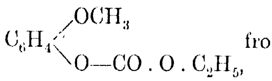
$$XONa + Cl . CO . NH_2 = NaCl + XO . CO . NH_2.$$

This process, besides being used for the pure substances, may also be applied to the mixture of phenols comprising creosote, by which means a mixture of neutral carbonic esters free from corrosive properties is obtained, which is called creosote carbonate.

Phenolic substances, such as guaiacol, can also be converted into alkyl carbonates instead of carbonates by the action of chloroformic ester on the hydroxyl compound or its sodium salt—

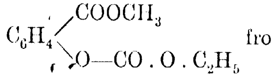
$$XONa + Cl . CO . O . C_2H_5 = X . O . CO . O . C_2H_5 + NaCl ;$$

e.g.—

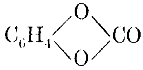


$$C_6H_4\begin{cases}OCH_3\\O—CO . O . C_2H_5,\end{cases}$$ from guaiacol,

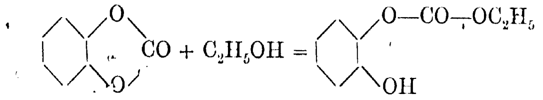
and



$$C_6H_4\begin{cases}COOCH_3\\O—CO . O . C_2H_5\end{cases}$$ from oil of wintergreen.

The carbonate of catechol,  $C_6H_4\begin{cases}O\\O\end{cases}CO$, forms addition products with compounds containing an alcoholic hydroxyl group or a primary or secondary amino group, whereby one of the hydroxyl groups of the catechol is regenerated with the formation of a mixed ester of carbonic acid.[2]

e.g.—



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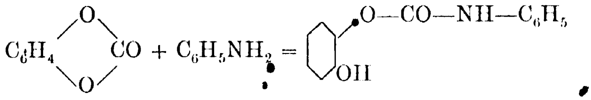
[1] D. R. P., 11,856, 116,366, for variations of this method.

[2] *Ibid.*, 92.535.

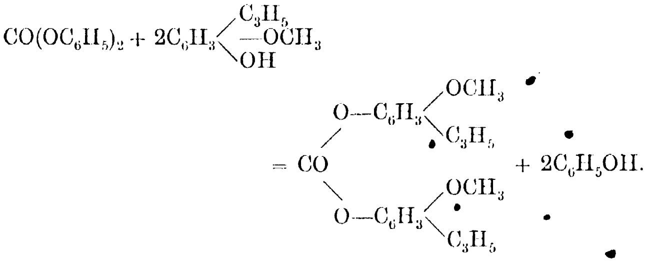
and



In the preparation of carbonates of phenols by the phosgene method, it may happen that those which are easily decomposed, such as the derivatives of iso-eugenol or menthol, are broken up, and therefore the method requires modification. In these cases, diphenyl or diethyl carbonate is first prepared, and this then made to react with the desired phenol.[1]

For example, with iso-eugenol—

$$COCl_2 + 2C_6H_5OH = CO(OC_6H_5)_2 + 2HCl,$$



$$CO(OC_6H_5)_2 + 2C_6H_3\begin{cases}C_3H_5\\—OCH_3\\OH\end{cases} = CO\begin{cases}O—C_6H_3\begin{cases}OCH_3\\C_3H_5\end{cases}\\O—C_6H_3\begin{cases}OCH_3\\C_3H_5\end{cases}\end{cases} + 2C_6H_5OH.$$

As the phosphites are said to be useful in the treatment of tuberculosis, it is not surprising that guaiacol phosphite, $P(—O—C_6H_4—OCH_3)_3$, has been prepared. It is a crystalline powder, which has the advantage over the carbonate and phosphate of guaiacol in being soluble in fatty oils, and it is prepared by suspending guaiacol and an equivalent of soda in alcohol and adding one molecular proportion of PCl_3 to the cooled mixture. It is then heated to boiling and the alcohol distilled off.[2] Substances such as this are known under the names of *Phosphatol*, *Creosote-phosphite*, etc.

Guaiacol benzoate is known as "*Benzosol*," and the acetate as "*Eucol*"; the cinnamate, which is known under the name of "*Styracol*," is said to be a very good antiseptic and anti-tubercular, free from harmful effects. *Cacodyliagol* is guaiacol cacodylate, $(CH_3)_2As . O . O . C_6H_4(OCH_3),H_2O$.

Another type of guaiacol derivatives is that in which the hydroxylic hydrogen is replaced by alkyl groups or other groups in which the hydroxylic oxygen is directly united to carbon. Veratrol may be included in this class, but it does not show the physiological action of guaiacol in any great degree, and probably does not split off any guaiacol in the organism. If, however, instead of replacing the hydrogen by a methyl group as in veratrol, one replaces it by a larger group, then the resulting compound is less stable, and guaiacol is regenerated to a greater or less extent in the organism. The glycerol ether of guaiacol—

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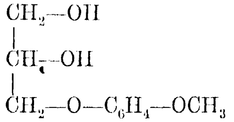
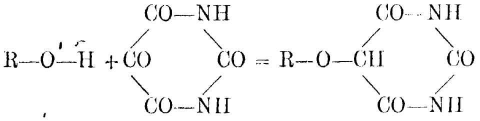
[1] D. R. P., 99,057.

[2] *Ibid.*, 95,578.



$$\begin{array}{l} CH_2—OH \\ | \\ CH—OH \\ | \\ CH_2—O—C_6H_4—OCH_3 \end{array}$$

known as "*Guaiamar*," is one of the most important of this type. It is soluble in water and is prepared by the action of mono-chlorhydrin, $CH_2(OH)—CH(OH)—CH_2Cl$, on an alkaline salt of guaiacol, or by the interaction of guaiacol and glycerol in presence of condensing agents. Glycerol ethers of other phenols have been prepared in the same manner. Tasteless soluble derivatives of guaiacol and other phenolic substances are obtained by the action of alloxan on phenols in presence of certain condensing agents, such as H_2SO_4, HCl, $ZnCl_2$, etc.[1]



An insoluble guaiacol preparation, known as "*Cetiacol*" or "*Palmaicol*," is obtained by the action of guaiacol in sodium ethylate on spermaceti oil at 80° C.[2] It is said to be without irritant action on the alimentary canal.

Guaiaperol is an addition product of guaiacol [illegible] piperidine, having the formula $C_5H_{11}N,(C_7H_8O_2)_2$. The [illegible]med at is to combine the action of guaiacol with the [illegible] piperidine on the heart and circulation. [illegible] without irritant action.[3]

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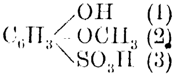
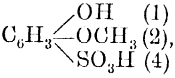
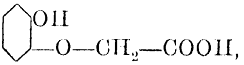
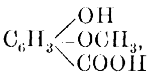
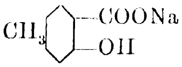
[1] D. R. P., 113,722. [illegible] or variations of this method.

[3] Chaplin and Tunnicliffe [illegible]

formaldehyde and creosote, and has been recommended as an internal antiseptic. A substance of this type recently introduced is "*Hexamecoll*," a preparation of guaiacol and hexamethylene-tetramine.[1] It is a powder which readily splits up into its components (*e.g.* when rubbed on the skin), and is recommended as an external disinfectant.

Another class of guaiacol derivatives comprises substances which do not regenerate guaiacol in the organism. It was to be expected that the entrance of a sulphonic acid group into guaiacol would lower its activity, and such is found to be the case. By sulphonating guaiacol at 70°-80° C.,  $C_6H_3{<}\begin{smallmatrix}OH & (1)\\ OCH_3 & (2)\\ SO_3H & (3)\end{smallmatrix}$ is obtained, which is therapeutically useful, its potassium salt known as "*Thiocoll*" being soluble and non-irritant. If the sulphonation be carried out at 140°-150° C., the chief product is  $C_6H_3{<}\begin{smallmatrix}OH & (1)\\ OCH_3 & (2)\\ SO_3H & (4)\end{smallmatrix}$, which is of no therapeutic value. The sodium salt of  known as "*Guaiacetin*," is soluble in water and nearly tasteless, and can be obtained by the action of chloracetic acid on catechol in the presence of alkali.[2] Guaiacol-carboxylic acid,  $C_6H_3{<}\begin{smallmatrix}OH\\ OCH_3\\ COOH\end{smallmatrix}$, is sparingly soluble, and has antiseptic properties, but has no advantage over guaiacol.

Although not a derivative of guaiacol, "*Solveol*" is used as a cheap substitute for guaiacol to which it has a similar action. It is a solution of creosols in sodium para-cresotinate—



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[1] *Cf.* Chap. XI.

[2] D. R. P., 87,386; see also *ibid.*, 87,668 and

CHAPTER XI.

OTHER ORGANIC ANTISEPTICS, EXCLUDING HALOGEN COMPOUNDS.

Organic Dyestuffs and Theories of Chemico-Therapy.—The organic dyestuffs are of interest both from the practical point of view on account of their use in therapeutics, and also on account of their importance in the development of the theories concerning the mode of action of drugs.

Many of the diseases caused by microbial or parasitic infection can be successfully treated by a suitable serum, but there are a large number, especially those of protozoal origin, which do not lend themselves to serum-therapy. In these cases a cure has been sought by chemical means, and at one time great hopes were entertained of curing many diseases of microbial origin by the use of general antiseptics, such as those which have proved so valuable in surgery. Generally speaking, however, the results obtained by the introduction of antiseptic methods into medicine have been disappointing when compared with the success which has attended their use in surgery. Various processes such as the intravenous injection of formaldehyde solutions, the inhalation of antiseptic vapours such as creosote for consumption, and many others, have not fulfilled the hope that was placed in them. This is not surprising when it is borne in mind that most antiseptics are quite as injurious to the tissues of the higher organism as they are to the bacteria (*cf.* Chap. X.). It has been pointed out[1] that a greater measure of success may be hoped for in the case of those diseases which are caused by protozoa rather than by bacteria. The latter are probably amongst the oldest living organisms, and have probably acquired a high degree of resistance, but the former do not appear to have been able to adapt themselves so successfully to their environment, and the diseases they give rise to are very likely of more recent date than those caused by bacteria.

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[1] Cushny, *Proc. Roy. Soc. Med.*, 2, iv. (1909), 49.

In some of these diseases favourable results have been obtained by the use of a chemical specific, which is not equally fatal to all forms of life, but which reacts specifically with certain micro-organisms in a manner somewhat analogous to the action of the afore-mentioned curative sera. This is expressed by saying that a substance of this type should have a strong affinity for the parasites (parasitotropic), but should be only slightly active to the organism (organotropic). Instances of this are afforded by syphilis and malaria, which yield far more readily to specific antisepsis, the former to mercury and arsenic and the latter to quinine, than do diseases of bacterial origin.

Our knowledge of the chemical specifics and their probable mode of action, we mainly owe to Ehrlich,[1] and his success in this field was largely due to a careful study of the reactions between the parasites and the dyes which reveal them in their surroundings. He realized that the relation between a dye and a particular type of cell is a chemical fact of great importance, and that such a dye must contain an anchoring group that can enable it to attach itself to the particular type of cell in question. To vary the simile, the chemical specific may be likened to a poisoned arrow, the point being the particular dye which has a selective affinity for the parasite, and therefore fixes it. If a poison can be attached to such a dye or to the anchoring group of such a dye, the arrow will be not merely a dye, but also the desired chemical specific.

This procedure is not so simple as might be gathered from the above, as the attachment of a poisonous element or radicle may destroy the anchoring effect of the other groups. On the other hand, many dyes are themselves poisonous to certain parasites, and act as chemical specifics in these particular infections.

For example, some of the triphenylmethane dyes, many of the azo dyes derived from benzidine, and various thiazine dyes, such as methylene-blue, have a strong parasiticidal action.

Thus, amongst the dyes derived from benzidine, Trypan Red and Trypan Blue have a strong trypanocidal[1] action. The former is obtained by tetrazotizing benzidine-orthosulphonic acid, and coupling with β-naphthylamine 3-6-disulphonic acid, and therefore has the formula :—

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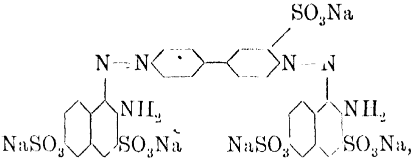
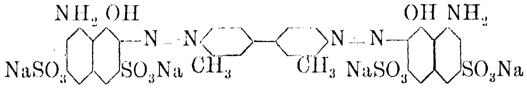
[1] *Cf.* Chap. I., p. 8.

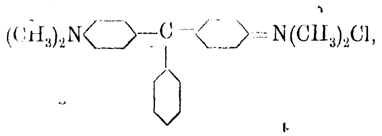


the latter is obtained by tetrazotizing *o*-tolidine, and coupling with 8-amino-naphthol (1), 3-6 disulphonic acid ("H" acid), and therefore is represented by the formula :—



It is noteworthy that all the azo dyes of this series which are effective trypanocides have the sulphonic acid groups in the 3-6 position. Naga Red which differs from Trypan Red only in the absence of the sulphonic acid group in the benzidine portion of the molecule was found to have a strongly poisonous action on the spirilla of relapsing fever, but it also acts strongly on the red blood corpuscles. Trypan Red and Trypan Blue have shown good results in the treatment of nagana, especially when used in conjunction with certain triphenylmethane dyes such as di- and tri-hydroxy malachite greens, and para-rosaniline.

Malachite Green has the formula :—



and Brilliant Green, which is the sulphate of the corresponding ethyl compound, is used fairly extensively as a general antiseptic.

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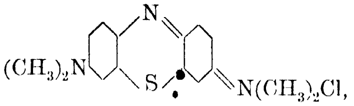
[1] The various species of trypanosomes are the cause of many tropical diseases, notably sleeping sickness, which is due to infection by *Trypanosoma gambiense*.

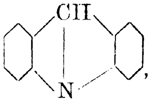
Methylene blue,



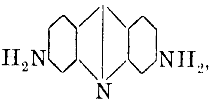
is used internally in a variety of conditions such as rheumatism, cystitis, nephritis, etc. This dye was found to have strong parasiticidal action on the spirilla of relapsing fever in test-tube experiments, but failed when used on infected animals.

A dye which is largely used as a paste for external application for stimulating the growth of epithelium over granulating wounds, is *Scarlet Red*, an azo dye derived from amidoazotoluene and β-naphthol, and therefore having the formula, $CH_3 . C_6H_4 . N : N . C_6H_3(CH_3) . N : N . C_{10}H_6O$.

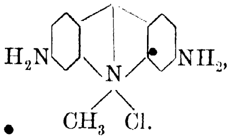
Some of the dyes derived from acridine,



have recently attracted considerable attention as antiseptics both for external and intravenous use, namely *Proflavine*, 3-6 diaminoacridine sulphate,



and *Trypaflavine or Acriflavine*, 3-6 diaminomethylacridinium chloride



The latter was originally introduced by Ehrlich as a trypanocide.

Proflavine is prepared[1] by the interaction of aniline, formaldehyde and caustic potash, and heating the resulting product with aniline hydrochloride, whereby diaminodiphenylmethane is formed. This is then nitrated, and the product reduced with tin and hydrochloric acid, and the reduction product which contains the tin double salt of tetra-aminodiphenylmethane,

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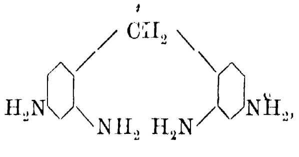
[1] Benda, *Ber.*, 45 (1912), 1787; D. R. P., 230,412; E. P., 24,6[illegible]2 (1910).



is heated in an autoclave at 140° to form 3-6 diaminoacridine.

To prepare Acriflavine from Proflavine,[1] the amino groups in the latter are protected by acetylation, and the diacetyl compound is then methylated by methyl sulphate or methyl toluenesulphonate in nitrobenzene solution. The acetyl groups are then hydrolyzed from the resulting compound by heating with hydrochloric acid, and on cooling the desired hydrochloride crystallises out in red needles.

Browning and his colleagues have recommended Proflavine and Acriflavine in the treatment of wounds, as they have high antiseptic power, together with freedom from irritant or toxic action, and no inhibiting effect upon the phagocytic action of the leucocytes or upon the process of healing. Up to the present, the clinical evidence appears to be very conflicting, but it is probable that good practical results will be obtained with these compounds.

Naphthalene, Pyridine, and Quinoline Derivatives.—The antiseptics derived from other cyclic systems, such as naphthalene, pyridine and quinoline, are none of them so important as certain benzene derivatives, such as phenol. The naphthols and their derivatives have already been mentioned in connection with the phenols, but naphthalene itself has antiseptic properties, and on account of its volatility is a useful insecticide, and has largely replaced camphor as a means of protecting clothes and other fabrics from moths. It is often sold for this purpose under the name of "carbon."

All the pyridine carboxylic acids have strong antiseptic properties. *Uvitonic acid* (2-picoline-4-6-dicarboxylic acid),

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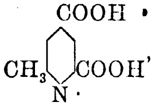
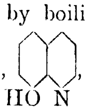
[1] Benda, *Ber.*, **45** (1912), 1795; D. R. P., 243,085.



is said to be a stronger antiseptic than salicylic acid, but the expense of its preparation has prevented it from being used for this purpose. It is produced by the action of alcoholic ammonia on pyruvic acid.[1]

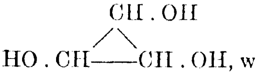
Quinoline has an antiseptic action, which is increased by the entrance of methyl groups. A quinoline derivative has been placed on the market under the name of *Chinosol*, and is prepared by boiling an alcoholic solution of ortho-hydroxy-quinoline,



with acid potassium sulphate.[2] The product appears to consist of ortho-hydroxy-quinoline sulphate and potassium sulphate. It has been used as an antiseptic both internal and external.

Various other quinoline derivatives are described in Chapter XV. (Uric Acid Eliminants).

Formaldehyde.—The strong antiseptic properties of formaldehyde have only recently been made use of in medicine, as the application of this substance has been hindered by its corrosive and toxic action. It readily polymerizes, forming tri-oxy-methylene,



$\mathrm{HO\,.\,CH}\overset{\mathrm{CH\,.\,OH}}{\diagup\diagdown}\mathrm{CH\,.\,OH}$

which is also strongly antiseptic, but gives rise to bad effects when taken internally. Formaldehyde has long been used for the disinfection of rooms, for which purpose its volatility renders it eminently suitable, but its use as a drug depends on the manufacture of compounds which slowly split off formaldehyde under the influence of the secretions of the organism.

One of the earliest compounds of this class was *Glutol*, obtained by the action of formaldehyde on gelatine; other compounds of this type have been prepared with formaldehyde and casein,[3] and formaldehyde and nucleic acid, the latter compound yielding soluble alkali salts.[4] The compounds of formaldehyde and carbohydrates are of greater importance. Classen found that formaldehyde reacts with starch, dextrin, etc., yielding insoluble, odourless, non-irritant substances, which slowly split off formaldehyde, and are antiseptic without being poisonous.[1] Soluble condensation products of dextrin and formaldehyde (*Dextroform*) can be obtained by a modification of this process.[2] A condensation product of formaldehyde with lactose has, under the name of *Formamint*, attained great popularity. This substance is used in the form of tablets, which, when allowed to dissolve in the mouth, liberate formaldehyde and so check and prevent septic conditions in the throat and mouth.

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[1] Böttinger, *Annalen*, **188** (1877), 330; **208** (1881), 138; *Ber.*, **13** (1880), 2032; De Jong, *Rec. Trav. Chim.*, **23** (1904), 136.

[2] D. R. P., 88,520.

[3] *Ibid.*, 13,565.

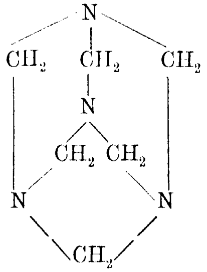
[4] *Ibid.*, 139,907.

Hexamecoll, a condensation product of guaiacol and hexamethylenetetramine, has been considered in the previous chapter.

Formaldehyde reacts readily with ammonia, forming *hexamethylenetetramine*, $(CH_2)_6N_4$, discovered by Butlerow[3] in 1860.

$$6CH_2O + 4NH_3 = (CH_2)_6N_4 + 6H_2O.$$

It is a basic substance, very soluble in water, and its constitution is probably represented by the formula—



This substance has strong antiseptic properties, but its aqueous solutions can be taken internally without causing poisonous or irritant symptoms. It is largely used in medicine, under the names of *Hexamine*, *Urotropin*, *Cystamine* and *Cystogen*, as a urinary antiseptic, for which purpose it is stated to be better than salicylic acid or any of the older preparations. It has some solvent action on uric acid, but it is improbable that it is capable of dissolving uric acid to any extent in the concentrations in which it can be present in the organism (*cf.* Chapter XV.). It is also said to be of value in laryngitis, pharyngitis, etc. The anhydromethylene-citric-acid—

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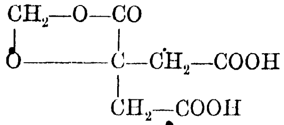
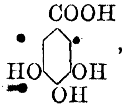
[1] D. R. P., 92,259, 93,111, 94,628, 99,378.
[2] *Ibid.*, 94,282. [3] Butlerow, *Annalen*, **115** (1860), 322.



derivative of urotropine has been introduced under the names of *New Urotropin* and *Helmitol.*

A large number of other derivatives and additive products of hexamine have been introduced into medicine as urinary antiseptics. For example, *Amphotropin* is hexamine camphorate, and the additive compounds of hexamine with sodium acetate, sodium citrate, and sodium benzoate are known respectively as *Cystopurin, Formurol,* and *Cystazol.* In the last-named, the antiseptic properties of the sodium benzoate are added to those of the hexamine.

Tannic and Gallic Acids.—Tannic acid is distinguished by its astringent and styptic action, and its freedom from toxic effects; gallic acid is more irritant and five times as antiseptic as tannic acid.[1] Gallic acid has the structure,



, but that of tannic acid is not known with certainty. Its empirical formula is $C_{14}H_{10}O_9$, from which it appears to be a *di*gallic acid.

In order to avoid the unpleasant taste of tannic acid itself, various insoluble derivatives have been prepared, which pass unchanged through the stomach, and are decomposed in the intestine, where they liberate free tannic acid. *Tannigen* is an insoluble acetyl derivative of tannic acid, soluble in alkalies.[2] *Tannoform,* one of the best examples of this class, is a condensation product of tannic acid and formaldehyde.[3]

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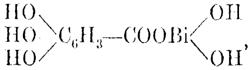
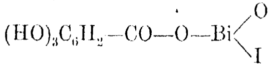
[1] Heinz and Liebrecht, *Ber. klin. W.* (1891), 584.
[2] D. R. P., 78,879; H. Meyer, *Deut. med. W.*, 31 (189[illegible]).
[3] D. R. P., 88,082.

$$2C_{14}H_{10}O_9 + HCHO = CH_2(C_{14}H_9O_9)_2 + H_2O.$$

It combines the antiseptic properties of formaldehyde with the astringent action of tannic acid, and is used internally as an astringent and antidiarrhœic; externally it is used as an antiseptic for wounds, etc.

Similar preparations of gallic acid have been devised, but the compounds of this acid containing bismuth are of more importance. Bismuth has a beneficent action on wounds, causing the surface to dry without impairing the healing power,[1] and therefore its insoluble compounds with antiseptic and astringent substances readily lend themselves for use as iodoform substitutes (*cf.* next chapter).

Dermatol is basic bismuth gallate,  $\begin{matrix}HO\\HO\\HO\end{matrix}\!>C_6H_3-COOBi<\!\begin{matrix}OH\\OH\end{matrix}$, and is a favourite iodoform substitute.

Airol is a derivative of Dermatol, in which one of the hydroxyl groups attached to the bismuth is replaced by an iodine atom,[2]  $(HO)_3C_6H_2-CO-O-Bi<\!\begin{matrix}OH\\I\end{matrix}$. In presence of moisture, it liberates free iodine, and it can therefore be regarded as a true iodoform substitute, owing its antiseptic action to the actual liberation of iodine. The presence of the bismuth and gallic acid confers also an astringent action on this substance. It is used externally as an iodoform substitute (*cf.* Chapter XII.).

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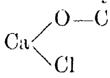
[1] Steinfeld and H. Meyer, *A. e. P. P.*, 20 (1886), 40.

[2] D. R. P., 80,399, 82,593.

CHAPTER XII.

HALOGEN ANTISEPTICS AND OTHER HALOGEN COMPOUNDS.

CHLORINE COMPOUNDS.

THE strong germicidal properties of chlorine and of hypochlorous acid have long been known. Bleaching powder, which is essentially a compound of calcium chloride and hypochlorite,  $Ca\begin{cases}O-Cl\\Cl\end{cases}$, has been used extensively for many years as a disinfectant, for which its cheapness renders it very suitable. Sodium hypochlorite, NaOCl, is readily soluble in water, but its caustic and irritant properties prevented its use as an antiseptic for the dressing of wounds. Recently, however, it has been shown by Carrel and Dakin that solutions of sodium hypochlorite to which boric acid has been added are far less irritant, and very good results have been obtained with such solutions in the treatment of infected wounds. The name "*Eusol*" has been applied to this solution. Nevertheless, these solutions still possess irritant properties, and a further improvement in this respect was effected by substituting sodium bicarbonate for the boric acid. This modified form of Dakin's solution is prepared by the action of a solution of sodium carbonate and sodium bicarbonate on bleaching-powder, and care must be taken that it contains from 0·45 per cent. to 0·5 per cent. of sodium hypochlorite. It has been very largely used with great success for the irrigation of wounds.

More recently, organic chloramines have been introduced by Dakin as substitutes for sodium hypochlorite. These substances were first discovered[1] and investigated by Chattaway and are prepared by the action of hypochlorite solutions upon organic compounds containing the imino (—NH—) or amino (—NH_2) groups, whereby chloramines containing the (—NCl—) group, and dichloramines containing the (—NCl_2) group, are produced. Physiologically, their action resembles that of hypochlorite, but therapeutically they possess many advantages over it. For example, they are far less irritant, and are stable solids which can be dissolved in water to give solutions of a definite strength, whereas sodium hypochlorite cannot be kept in the solid state, and its solutions are always of somewhat uncertain strength.

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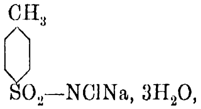
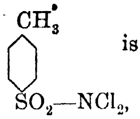
[1] Chattaway, *J. C. S.*, 87 (1905), 145.

The best known and most used of these chloramines is the substance introduced under the name of *Chloramine T.*[1] It is sodium *p*-toluenesulphonchloramide,  $CH_3C_6H_4SO_2$—NClNa, $3H_2O$, and is prepared from *p*-toluenesulphonyl chloride, a by-product in the manufacture of saccharin. This by treatment with ammonia is converted into *p*-toluenesulphonamide, which on warming with sodium hypochlorite solution is converted into Chloramine T.

$$CH_3 . C_6H_4 . SO_2Cl \rightarrow CH_3 . C_6H_4 . SO_2 . NH_2 \rightarrow CH_3 . C_6H_4 . SO_2NClNa.$$

It is also prepared by dissolving Dichloramine T (see below) in hot caustic soda solution.[2] This substance is also known by the trade name of *Tolamine.*

It is a stable crystalline compound which is soluble in water, and has been of great value in a variety of septic conditions, especially in military surgery for the treatment of infected wounds. Its freedom from irritant properties has rendered it particularly useful in the treatment of injuries to the mouth and jaw. It is also used as a disinfectant lotion in cases of infectious disease such as scarlet fever, measles etc.

The corresponding dichloramine, *p*-toluenesulphondichloramide,  is also used as an antiseptic under the name of *Dichloramine T*.

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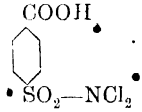
[1] Dakin, Cohen, Daufresne and Kenyon, *Proc. Roy. Soc.*, **B 89** (1916), 232; Dakin, Cohen, and Kenyon, *B. M. J.* (1916), 160.

[2] Chattaway, *loc. cit.*

It is readily prepared by dissolving *p*-toluenesulphonamide in bleaching powder solution, or by the action of hypochlorous acid upon Chloramine T.

It is used for the treatment of wounds[1] in the form of a solution in solvents such as "chlorcosane" (chlorinated paraffin wax) and chlorinated eucalyptol. Its oil solution has also been used as a naso-pharyngeal sterilizer in cases of meningitis, and complete sterilization of the carrier has been claimed by this means.

Another dichloramine derived from *p*-toluenesulphonamide is *p*-sulphondichloraminobenzoic acid, . This substance is known as *Halazone*, and is specially recommended for the sterilization of drinking water.[2] It is prepared by heating *p*-toluenesulphonamide with bichromate and sulphuric acid, whereby the methyl group is oxidized to the carboxyl group with formation of *p*-sulphonamino-benzoic acid. This acid is then dissolved in caustic soda solution, and treated with chlorine gas in the cold to form the desired dichloramino acid.

$$CH_3 . C_6H_4 . SO_2 . NH_2 \rightarrow COOH . C_6H_4 . SO_2 . NH_2 \rightarrow COOH . C_6H_4 . SO_2 . NCl_2.$$

Iodine Compounds.

Iodoform and its Substitutes.—Iodoform has been very extensively used in surgery as a dressing for wounds, as it seems to promote healing as well as exerting an antiseptic action. In laboratory experiments *in vitro*, iodoform has so slight a bactericidal power as to indicate that it would be useless for such a purpose, and its antiseptic action appears to be due to the free iodine liberated when it comes into contact with fat, putrefactive material, etc.

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[1] Dakin and Dunham, *Pharm. Journal*, 100 (1918), 82.
[2] *Ibid.*, *B. M. J.* (1917), 683.

Iodoform is prepared according to a well-known method by the action of free iodine on a warm mixture of acetone or alcohol and sodium hydroxide or carbonate solution. In this process, part of the iodine is used up in forming alkaline iodide, from which free iodine has to be again regenerated before it can be used for the manufacture of a further quantity of iodoform. For this reason, various electrolytic methods for preparing iodoform have been devised. One of these consists in electrolyzing in a current of carbon dioxide a warm solution of potassium iodide to which alcohol has been added.[1]

The same method can be applied to the preparation of chloroform and bromoform, but in these cases the stream of carbon dioxide is unnecessary. Iodoform is also manufactured by passing ozone through a solution of potassium iodide and sodium carbonate in 30 per cent. alcohol, at a temperature of 50° C. The ozone is passed into the liquid until all the potassium iodide has been decomposed.[2]

Iodoform, in spite of its many valuable properties, suffers from some serious drawbacks, the chief of these being its powerful odour and the fact that it often has an irritant action on the skin, giving rise to a kind of eczema. It also has toxic properties, which sometimes give rise to definite symptoms of poisoning. In order to mask the odour of iodoform, many preparations have been introduced in which it is mixed with strong and pleasantly scented substances, but these need not be mentioned here. On the other hand, by combining iodoform with inodorous substances, its volatility can be lowered and its odour destroyed.

For example, a compound of iodoform with hexa-methylene-tetramine is inodorous, and is known as *iodoformin*,[3] and a similar compound with hexamethylene-tetramine-ethyl iodide was introduced under the name *iodoformal*,[4] but both of these compounds are decomposed by water into their components, and hence in practice they possess no advantage over a mere mixture.

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[1] D. R. P., 29,771.

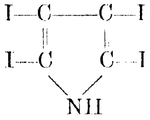
[2] *Ibid.*, 109,013.

[3] *Ibid.*, 87,812.

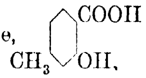
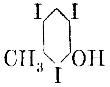
[4] *Ibid.*, 89,243.

Of far greater importance are the efforts that have been made to produce other insoluble compounds which should possess the valuable properties of iodoform in promoting the healing of wounds, and have the further advantage of being less irritant and toxic than iodoform, and free from any powerful odour. Many substances have been prepared in attempting to meet these requirements, and these comprise derivatives of iodine as well as those of other halogens and of various metals such as bismuth. Of the various iodine derivatives, pure and simple, that have come into use, only one of them, *iodol* (tetraiodo-pyrrol), resembles iodoform in the fact that its action is due to the actual liberation of iodine. *Airol*, a bismuth compound, which also liberates free iodine, has been considered in the previous chapter.

In aromatic compounds it is true that the antiseptic power is generally increased by the replacement of hydrogen by iodine, but nevertheless the latter is too firmly united to the nucleus to be liberated by the action of the tissues, and therefore these compounds cannot be compared in their action with iodoform. In the case of the pyrrol ring, however, the iodine is in a more labile state, and tetraiodo-pyrrol—



resembles iodoform in its action, and has the advantage of being odourless and non-irritant, as well as insoluble. It is used as an iodoform substitute under the name of *iodol*, and is prepared by the action of iodine on an alkaline solution of pyrrol, the latter being obtained from "bone-oil."[1]

There are, however, many other organic derivatives of iodine which possess antiseptic properties, and are used as iodoform substitutes, although their mode of action is quite different. For example, by the addition of a solution of iodine in potassium iodide to an alkaline solution of a phenol, compounds are produced containing two atoms of iodine, one of which replaces a nuclear hydrogen atom, and the other the hydrogen of the ydroxyl group. By the action of sodium sulphite, the iodine tom can be removed from the OI group and the mono-iodo-ubstituted phenol formed. A different type of iodophenol produced by the action of iodine in potassium iodide on henol-carboxylic acids in presence of an exact amount of lkali, whereby the COOH group is removed by loss of CO_2, nd iodine enters the nucleus but not the hydroxyl group.[1] or example,  ,when treated in this way, yields tri-odo-meta-cresol,  . The same product may also be repared by adding a solution of iodine in potassium iodide to very dilute solution of meta-cresol in alkali.[2]

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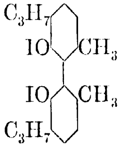
[1] D. R. P., 35,130, 38,423.

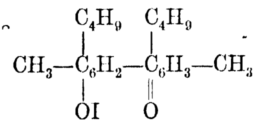
The iodoxyl compounds, containing the group —OI, possess arked antiseptic and anti-syphilitic properties, but the iodo-henols containing iodine in the nucleus do not differ very uch from the phenols in their action, but they are sometimes sed, as they are convenient crystalline insoluble antiseptics.

The best known of the iodoxyl compounds is *Aristol*, di-hymol-diodide—[3]



hich is a favourite antiseptic, but suffers from the drawback of being rather unstable and expensive.[4]

Europhen—



$$\begin{array}{ccccccc} & & C_4H_9 & & C_4H_9 & & \\ & & | & & | & & \\ CH_3 & — & C_6H_2 & — & C_6H_3 & — & CH_3 \\ & & | & & \| & & \\ & & OI & & O & & \end{array}$$

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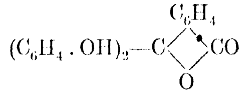
[1] D. R. P., 72,996. [2] *Ibid.*, 106,504. [3] *Ibid.*, 49,739.

[4] Eichhoff, *Monatsh. f. pr. Derm.* (1890), 2; Neisser, *Berl. klin. W.* (1890), Nr. 19.

is another substance of this type which serves as an odourless and non-irritant iodoform substitute.[1]

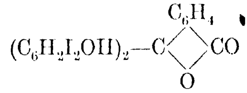
Tri-iodo-cresol, known by the fancy-name of *Losophan*, is an example of a phenolic compound in which the hydrogen atoms of the nucleus are replaced by iodine. These substances possess the antiseptic properties of phenols in an enhanced degree, but they cannot be regarded as iodoform substitutes, as they do not possess the characteristic iodine action, and are also too corrosive in their action on the skin.

Tetra-iodo-phenolphthalein has been prepared by many different methods.[2] Phenolphthalein itself—



$$(C_6H_4 . OH)_2—C\overset{C_6H_4}{\underset{O}{\langle\;\rangle}}CO$$

when taken internally has a mild purgative action, but is otherwise physiologically inert; but the tetra-iodo-derivative—



$$(C_6H_2I_2OH)_2—C\overset{C_6H_4}{\underset{O}{\langle\;\rangle}}CO$$

called *Nosophen*, has powerful antiseptic properties. As this substance contains two hydroxyl groups, salts can be prepared with the heavy metals such as zinc, iron, mercury, and bismuth, but these have not come into use, although they combine the antiseptic action of nosophen with the useful properties of the metal.

Isoform is the name that has been given to para-iodoxy-anisol, $CH_3\langle\quad\rangle IO_2$, a colourless insoluble powder that has been recommended as a dry antiseptic, and which is said to be especially valuable in the treatment of mercurial stomatitis.[3] It is obtained by the oxidation of para-iodo-toluene, $CH_3\langle\quad\rangle I$, whereby $CH_3\langle\quad\rangle ICl_2$ or $CH_3\langle\quad\rangle IO$ is formed, either being easily oxidized to $CH_3\langle\quad\rangle IO_2$.[4] Commercially, it is not met with in the pure state, but owing to its explosive nature is mixed with calcium phosphate or glycerol.

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[1] D. R. P., 56,830, 61,575.

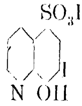
[2] Classen, *Ber.*, 28 (1895), 1606; D. R. P., 85,930, 86,069, 88,390; Kalle & Co., D. R. P., 143,596.

[3] Siebert, *Deut. med. W.*, 7 (1907), 256.

[4] D. R. P., 161,725.

Sozoiodol, $C_6H_2I_2(OH)(SO_3H)$,[1] probably owes its antiseptic action partly to its strongly acid character. Its zinc and mercury salts are useful preparations for the administration of these metals.

Loretin is iodo-hydroxy-quinoline sulphonic acid—



prepared by Claus by the sulphonation of hydroxy-quinoline with fuming sulphuric acid, and treating the reaction-product with iodine.[2] This substance is said to be an iodoform substitute free from unpleasant effects. Its sodium salt has been used in tuberculosis under the name of *Griserin*.[3] Other similarly constituted compounds with the same kind of action have been prepared, and iodo-chlor-hydroxy-quinoline[4] has been introduced as a non-poisonous iodoform substitute under the name of *Vioform*.

Substitutes for Alkaline Iodides.—Another important class of iodine compounds includes those substances which have been prepared with the object of producing substitutes for the alkaline iodides. The latter are largely used in medicine, but are liable to cause unpleasant symptoms, to which the term "iodism" is given, and for this reason a very large number of drugs have been introduced with the object of furnishing substances which should possess the therapeutic value of the alkaline iodides without giving rise to the symptoms of iodism.

Iodoform has been used internally, being for the most part converted by the organism into alkaline iodides, but it has no real value in this respect. Compounds of iodine (and of bromine) with fats which gradually split off their iodine appear to be very good substitutes for the alkaline iodides, compared with which they are said to possess many advantages.[5]

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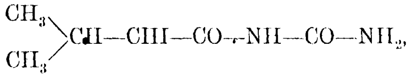
[1] D. R. P., 45,226.
[2] *Ibid.*, 72,942.
[3] *Apoth. Ztg.* (1904), 908.
[4] D. R. P., 117,767.
[5] H. Winternitz, *Deut. med. W.*, 23 (1897).

Iodipin is one of the best known substances of this type, and is a combination of iodine and sesame-oil.[1]

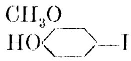
Iothion is di-iodo-hydroxypropane, $C_3H_5I_2OH$, and is used in the form of ointments as a substitute for tincture of iodine.

Iodival is mon-iodo-isovaleryl-urea—



$$\begin{matrix}CH_3 \\ CH_3\end{matrix}\!\!>\!CH{-}CHI{-}CO{-}NH{-}CO{-}NH_2,$$

and is administered internally as a substitute for iodine and the iodides. It is said to be specially useful in nervous diseases, and in syphilis.

Para-iodo-guaiacol,[2]  $HO\langle\;\rangle{-}I$ (CH_3O above), is decomposed into its components in the intestine, and has been recommended as a substitute for the iodides.

The thyroid gland contains iodine in organic combination, and various attempts have been made to prepare a similar substance to the so-called "iodo-thyrine" by combining iodine with proteins. The products thus obtained do not resemble iodo-thyrine in their physiological effects, but they form useful substitutes for the alkaline iodides. Compounds of iodine with proteins are readily obtained by the addition of iodine in potassium iodide solution to aqueous protein solutions, or by adding finely powdered iodine to warm aqueous solutions, and coagulating the product with acetic acid.[3] One of the best known compounds of this type is *Iodoglidine*, a compound of iodine with gliadin, the vegetable protein obtained from wheat. It behaves in a similar manner to potassium iodide, but is said also to increase the metabolism, thus resembling iodo-thyrine in this respect.[4] Another compound of iodine and protein is *Iodalbin*, which is also used as a substitute for the alkaline iodides.

BROMINE DERIVATIVES.

As in the case of iodine, the entrance of [illegible] into aromatic compounds increases their antiseptic power, but the chloro- and bromo-phenols have so strong an irritant action that derivatives of that type have found no therapeutic application.

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[1] Merck, D. R. P., 159,748.

[2] *Chemiker Zeitg.*, 31 (1907), 175.

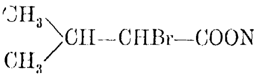
[3] Hopkins and Brook, *Journ. of Physiol.*, 22 (1897), 18[illegible].

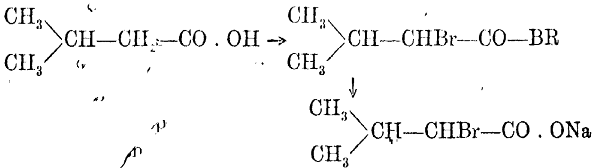
[4] *Deut. med. W.*, 37 (1907), 1490.

On the other hand, the alkaline bromides are of very great medicinal value, being especially important in the treatment of certain nervous disorders. Potassium bromide has some drawbacks precisely similar to those attending the use of potassium iodide, and so efforts have been made to find substitutes which will possess the useful sedative properties of potassium bromide without its drawbacks.

The substances here described are therefore not antiseptics, but are nervous sedatives and mild hypnotics. They are included in this chapter on account of their close chemical relationship to the iodine compounds described in the previous section, though they are therapeutically related to the hypnotics described in Chapter IV.

Bromipin is analogous to iodipin, and is said to be a valuable substitute for potassium bromide.

Valerobromine,  $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH{-}CHBr{-}COONa$, is said to be free from the drawbacks of potassium bromide, while retaining its sedative properties. It is also said to derive a sedative action from the presence of the valerianic acid grouping, but this seems doubtful. It is obtained by the action of bromine on valerianic acid, whereby bromo-valerianic bromide is obtained, which is then hydrolyzed with water and neutralized, giving Valerobromine—



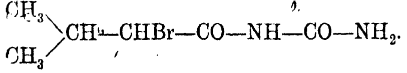
$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH{-}CH_2{-}CO\,.\,OH \rightarrow \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH{-}CHBr{-}CO{-}BR$$

$$\downarrow$$

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH{-}CHBr{-}CO\,.\,ONa$$

Other derivatives of α-bromoisovalerianic acid which are used as nervous sedatives are its ester with borneol,

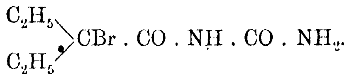
$C_4H_8Br{-}COOC_{10}H_{17}$, and its urea derivative,



$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>CH{-}CHBr{-}CO{-}NH{-}CO{-}NH_2.$$

The former is known as *Brovalol* and *Eubornyl.* The latter, which is exactly analogous to *Iodival* in constitution, is known by the names of *Bromurul* and *Dormigene.*

Another bromine derivative of urea which is used as a safe hypnotic is *Adalin,*[1] bromdiethylacetylurea,



$$\begin{matrix} C_2H_5 \diagdown \\ \end{matrix}\!\!\!\!\!\!\!\!\!\!\!\!\!\! \begin{matrix} \\ C_2H_5 \diagup \end{matrix} CBr\ .\ CO\ .\ NH\ .\ CO\ .\ NH_2.$$

In this compound, the mild hypnotic action of the

$$—CBr\ .\ CO\ .\ NH\ .\ CO\ .\ NH_2$$

group is probably enhanced by the presence of the two ethyl groups united to it (*cf.* Chapter IV.).

Bromoglidine is a compound of wheat protein with bromine, and *Bromalbin* is another bromine derivative of protein. Both are used as substitutes for the alkaline bromides, and they are respectively analogous to *Iodoglidine* and *Iodalbin.*

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[1] E. P., 2888 (1910).

CHAPTER XIII.

INORGANIC ANTISEPTICS AND METALLIC COMPOUNDS.

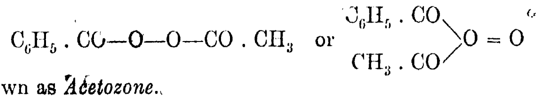
Most of the non-metallic inorganic antiseptics, like the chlorine compounds described in the previous chapter, owe their antiseptic properties to their oxidizing power. Practically the only exception is boric acid, H_3BO_3, which is a very weak antiseptic.

Hydrogen peroxide, H_2O_2, is a very useful antiseptic and disinfectant. In the presence of wounds and septic conditions it is decomposed into water and nascent oxygen, and has the great advantage of being odourless, non-poisonous, and almost free from irritant action. Other advantages of hydrogen peroxide are that it does not precipitate protein, and leaves only water when it has exerted all its antiseptic action.

A 30 per cent. neutral solution of hydrogen peroxide is known as *Perhydrol*. The peroxides of the alkaline-earth metals may be regarded as derivatives of hydrogen peroxide, and *Magnesium-Perhydrol* or *Biogen* (a mixture of MgO and MgO_2) and *Zinc-Perhydrol* or *Ektogen* (a mixture of ZnO and ZnO_2) are used as antiseptics; the former is for internal and the latter for external use.

Another compound of this type which may be regarded as a derivative of hydrogen peroxide is sodium perborate, $NaBO_3,4H_2O$, known as *Perborax*.

Various organic derivatives of hydrogen peroxide have been prepared, but as they owe their antiseptic properties solely to the liberated oxygen, they have not been considered in the chapters devoted to the true organic antiseptics. An example of this type is benzoyl-acetyl hydrogen peroxide—



$$C_6H_5 . CO{-}O{-}O{-}CO . CH_3 \quad \text{or} \quad \begin{matrix} C_6H_5 . CO \\ CH_3 . CO \end{matrix}\!\!>\!O = O$$

known as **Acetozone.**

For a similar reason, various metallic salts of organic acids are also included in this chapter, rather than in that on the organic antiseptics, as their action depends on the metal and not on the organic acid radicle.

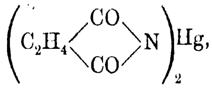
Derivatives of Mercury.—Mercury compounds are used very considerably as antiseptics, and also in the treatment of syphilis. The part played by antiseptics in the specific treatment of protozoal diseases was discussed in Chapter XI., and in this section a description is given of the various preparations of mercury, and the *raison d'être* of their existence.

As antiseptics, mercury salts suffer from the drawback that metallic instruments cannot be immersed in them, and for the treatment of syphilis, their corrosive, irritant and toxic nature is a serious disadvantage. For this reason, many efforts have been made to prepare soluble mercury salts which can be injected without giving rise to the bad effects of the simple soluble salts, such as the chloride. In another direction, attempts have been made to obtain soluble mercuric salts in which the electronegative character of the mercury is masked, so that solutions may be used for the sterilization of metallic instruments without the former being reduced with liberation of metallic mercury. Another drawback of mercuric chloride is the fact that it is not very soluble, and only dissolves slowly.

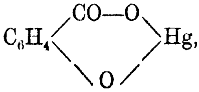
A method of administering mercury which has found a good deal of favour is by intramuscular injections of calomel (mercurous chloride, Hg_2Cl_2), and of metallic mercury. For example, "*Lambkin's Cream*" (No. 1) consists of an emulsion of 5 grams calomel and 20 grams "creocamph" made up to 100 c.c. with palmitine or carbolized liquid paraffin. The "creocamph" is a mixture of equal parts creosote and camphoric acid, and is used to minimize pain at the site of the injection. This cream (No. 1) is followed by No. 2 which resembles it except that the 5 grams of calomel are replaced by 10 grams of free mercury.

A stronger medium is "*Grey Oil*" which contains 40 grams of metallic mercury, 26 grams of lanoline, and 60 grams of vaseline, this being 40 grams of mercury to 100 c.c. compared with 20 grams to 100 c.c. in the case of Lambkin's Cream, No. 2.

Sometimes the older method of using mercurial ointment (the oleate or the free metal) is preferred, in spite of the indefinite amount of mercury that is absorbed through the skin, as compared with the exact amount administered by intra-muscular injection. Colloidal metallic mercury[1] has been tried as an injection medium, and various phenolic derivatives of mercury have been prepared,[2] such as the mercury salts of phenol, naphthol, resorcinol, and tribromophenol, but these latter do not appear to be suitable for injection. The dimethyl, diethyl, and diphenyl derivatives of mercury are too dangerously toxic to be of any therapeutic value. Most satisfactory results seem to have been obtained with mercury derivatives of acid-amides, and amino-acids. Mercury derivatives of formamide, $(H . CO . NH—)_2Hg$, and of succinimide as well as those



of asparagine, $[NH_2 . CO—CH(NH_2) . COO]_2Hg$, and alanine, $[CH_3—CH(NH_2)—COO]_2Hg$, have been prepared. Of these, mercury succinimide has been used in medicine under the name of *Hydrargol.*

Good results are said to have been obtained with secondary mercury salicylate, , a substance from which the mercury cannot be precipitated with H_2S. Although this compound is itself insoluble in water, it yields soluble double salts with the alkali chlorides. Mercurous tartrate, prepared by Lustgarten, is decomposed by the intestinal alkali, with liberation of finely divided mercury.

Of the various injection media that have been tried, the best results, so far, appear to have been obtained with various protein preparations. Some of these, obtained from glue, are soluble in water in any quantity, and are not precipitated by protein, nor acted on by alkalies with liberation of mercury (*cf.* Silver).

The mercury salt of para-phenol-sulphonic acid, known as

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[1] Lottermoser, *Journ. prakt. Chem.*, 57 (1898), 484.
[2] D. R. P., 48,539.

Hydrargyrol, $(\mathrm{HO}\langle\ \rangle\mathrm{SO_2{-}O{-}})_2\mathrm{Hg}$, is said not to precipitate proteins, and not to attack metallic instruments. A double salt of this substance and ammonium tartrate is more stable $\mathrm{C_{12}H_{10}O_8S_2Hg, 4[C_4H_4O_6(NH_4)_2] + 8H_2O}$,[1] and has been introduced into practice under the name of *Asterol*. It is soluble in water, giving a clear neutral solution, from which H_2S does not precipitate HgS. It is stated that aqueous solutions of asterol do not precipitate albumen,[2] and though the bactericidal action is only about half that of mercuric chloride, the solutions have the advantage of not losing any of their power in protein fluids, and of penetrating further into the tissues than solutions of sublimate. Asterol does not cauterize wound surfaces, and does not injure metallic instruments, and on account of these numerous advantages it is recommended for general surgical use.

Thymegol is a substance of a similar type to *Hydrargyrol*, and is the mercury potassium salt of thymol *p*-sulphonic acid.

Similar preparations have been obtained by the action of mercuric oxide on alkaline solutions of phenol-*di*sulphonic acid in molecular proportions.[3] They are termed *Hermophenyl*, and are soluble in five parts water. Potassium mercury hyposulphite is also said to be non-irritant and easily soluble.[4]

Hydrargotin is mercury tannate, and *Toxynone* is sodium *m*-acetylaminomercuribenzoate,

$$\mathrm{HO{-}Hg{-}C_6H_3(NH\,.\,CO\,.\,CH_3)(COONa)}.$$

Soluble mercury preparations which do not attack metallic objects have long been used in this country in the form of potassium mercury iodide, to which alkaline carbonate has been added. Similar compounds have been introduced in Germany by adding mercuric cyanide, cyanate, or *p*-phenol-sulphonate to alkaline carbonates.[5]

Silver.—Silver nitrate, besides its well-known caustic action, possesses strong bactericidal properties, but as it is precipitated both by proteins and by chlorides, its use is confined to the surface of the body. It would be desirable to obtain a compound of silver which, while retaining its bactericidal properties, should be free from the caustic action of silver nitrate, and not be precipitated by chlorides or proteins. Brief mention need only be made of colloidal silver chloride and colloidal silver solutions, which were at one time in great vogue for disinfection of the tissues by intravenous injection. Such methods are useless, as the damage done to the tissues is greater than to the bacteria, and treatment of this kind is only justifiable for local infections (*cf.* following chapter).

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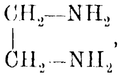
[1] D. R. P., 157,663.
[2] Steinmann, *Ber. klin. W.*, **11** (1899), 229.
[3] Lumière and Chevotier, *C. R.*, **132** (1901), 145.
[4] Dreser, *A. e. P. P.*, **32** (1893), 456.
[5] D. R. P., 104,904, 121,656.

These colloidal solutions, as also solutions of silver phosphate in ethylene-diamine, fulfil most of the chemical requirements outlined above, but they suffer from various drawbacks which have prevented their general application. The compound of silver nitrate and ethylene-diamine,



$$\begin{array}{l} CH_2-NH_2 \\ | \\ CH_2-NH_2 \end{array}$$

, however, is used as a substitute for silver nitrate under the name *Argentamin.*

As in the case of mercury, better results have been obtained with protein compounds. *Argonin* is a compound of silver and casein, but is difficultly soluble in water and sensitive to light. *Protargol* is a compound of this type which has a higher percentage of silver, is free from caustic effects, does not precipitate chlorides, and has the bactericidal effects of silver. To prepare it, a peptone solution is precipitated with silver nitrate solution or shaken with moist silver oxide, and the insoluble compound thus obtained, digested with protalbumose. Soluble protargol is formed in this way, and is separated from the solution by evaporation *in vacuo.* Similar compounds can be obtained from plant globulins, and the corresponding compounds have also been obtained from mercury, iron, copper, lead, zinc, and bismuth.[1] Other silver albumin compounds have been obtained from gelatoses (hydrolytic products from glue).[2] *Albargin*, a powder readily soluble in water and of neutral reaction, is a substance of this type. It is recommended in various septic conditions as a non-irritant antiseptic.

Protosil is another silver protein compound, very soluble in water, and is not precipitated by chlorides or by protein. It contains about 20 per cent. of silver.

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[1] D. R. P., 118,353, 118,496.

[2] *Ibid.*, 141,967, 146,792, 146,793.

Nargol is a silver nucleinate, soluble in warm water, and contains about 10 per cent. of silver.

Zinc.—Many salts of zinc possess astringent and antiseptic properties. A soluble zinc salt, recommended for various different complaints as a non-irritant antiseptic, is *Nizin*,[1] a zinc salt of sulphanilic acid, $(NH_2—C_6H_4—SO_3)_2Zn, 4H_2O$.

Zinc perhydrol combines the antiseptic properties of hydrogen peroxide with the astringent properties of zinc, and has already been mentioned (p. 190).

Aluminium.—The astringent properties of ordinary alum are well known. The aluminium salt of β naphthol-disulphonic acid, $[C_{10}H_5OH(SO_3)_2]_3Al_2$, is an example of the various organic aluminium salts that have been prepared. It is known as *Alumnol*,[2] and is recommended as a mild antiseptic, etc.

Iron.—Ferric salts resemble those of aluminium in many of their properties, and they are used as astringents and styptics. For use as a styptic, a double compound of ferric chloride and antipyrine has been introduced under the name of *Ferripyrin*, but it has no advantages compared with ferric chloride itself.

The chief therapeutic use of iron is, however, in anæmia and chlorosis. For this purpose, the ferrous salts are usually preferred, as they do not have so great a caustic action as the ferric, and hence do not disturb the stomach so much. The unpleasant by-effects of iron on the teeth and stomach have led to many attempts at obtaining compounds which should be free from these disadvantages.

By the reduction of hæmoglobin, Kobert obtained a substance, *hæmol*, which contains the iron in the same form as hæmoglobin, and Bunge obtained from egg-yolk a substance from which the iron could not be precipitated by ammonium sulphide.[3] This substance was termed *hæmatogen* by Bunge, and a similar substance has been isolated from the liver.[4] A synthetic albuminate of iron was obtained by Schmiedeberg,[5] but this differs from Bunge's hæmatogen in certain respects. Various other albuminates of iron have been prepared, and many of these, as well as some of the foregoing substances, have been placed upon the market (*Hæmol*, *Hæmatogen*, etc.). None of these organic compounds are any more powerful agents in the treatment of anæmia than the simple inorganic salts, their advantage being simply that they are less irritant to the gastro-intestinal tract.

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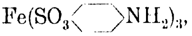
[1] *Apotheker Zeitung* (1908), 215.

[2] D. R. P., 74,209; *Ber. klin. W.*, **46** (1892).

[3] *Zeit. physiol. Chem.*, **9** (1884), 49.

[4] *Ibid.*, **10** (1886), 453.

[5] *A. e. P. P.*, **33** (1894), 101.

Recently, iron has been used with success in the treatment of syphilis (*cf.* "Arsenic Compounds," Chapter XIV.). The substance which has been found most useful in this respect is ferric sulphanilate,  $Fe(SO_3\langle\quad\rangle NH_2)_3$, known as *Ferrivine*.[1] It is a stable substance readily soluble in water.

Compounds of arsenic and antimony, as well as certain bismuth preparations, are dealt with elsewhere. (Chapter XIV., and pp. 128, 178).

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[1] McDonagh, *Lancet* (1916), 239.

CHAPTER XIV.

ARSENIC AND ANTIMONY COMPOUNDS.

Introduction.—Arsenious oxide and the salts derived from it have for many years been used as tonics and in the treatment of anæmia, while the irritant properties of antimony have long been made use of in potassium antimonyl-tartrate (tartar emetic). In this chapter, however, it is proposed to deal mainly with a modern development of the therapeutics of arsenic and antimony, namely, with their use in the treatment of diseases of protozoal origin, such as trypanosomiasis (sleeping sickness), syphilis, etc. This subject offers a very good example of the application of Ehrlich's views on chemico-therapy and the action of chemical specifics to which reference has already been made in Chapter XI. (pp. 170-173).

For the treatment of these diseases, the organic derivatives of arsenic, especially those containing an aromatic nucleus, have proved the most useful. In the case of antimony, its close resemblance to arsenic indicates the probability of its useful application in the same way, but up to the present, antimony compounds analogous to the most successful arsenic compounds have not been used.

Within recent years it has been shown that the "sleeping sickness" of tropical Africa is caused by a protozoal parasite, the *Trypanosoma gambiense*, and this disease was found to react to various specifics, such as arsenic, although unfortunately their clinical use has not been completely successful. It was found that certain organic preparations, of which atoxyl was one of the first to be extensively tried, appeared to be more satisfactory than the older inorganic preparations, such as Fowler's solution (potassium arsenite). Nevertheless atoxyl is devoid of action on the trypanosomes *in vitro*, and it can only become specific for them when it undergoes some change in the body. Most of the atoxyl passes through the body unchanged, but the small portion which becomes changed is apparently capable of destroying a large proportion of the parasites. Probably the arsenic in this portion is changed into some compound of an unknown nature, the same or a similar compound being also formed from part of the arsenic in inorganic preparations. Although the active therapeutic agent is therefore probably the arsenic content, it is no doubt true that atoxyl possesses advantages over inorganic preparations by virtue of its physical properties, such as solubility. It is possible that it is able to penetrate into tissues which cannot be readily reached by inorganic arsenic.

Organic arsenic preparations of this type have also been used for the treatment of syphilis, but atoxyl does not appear to be so useful as mercury in this respect, although excellent results have been obtained with some of the newer preparations such as Salvarsan and its derivatives, especially when used in conjunction with mercury.

Antimony possesses somewhat similar pharmacological properties to arsenic, and on investigation antimony[1] was found to have an even stronger trypanocidal action than arsenic, but its inorganic preparations labour under the disadvantage of being strongly irritant, while organic preparations of antimony analogous to atoxyl are difficult to prepare, and are not effective therapeutically.

Bismuth also has a powerful trypanocidal action, but it appears to be too toxic to the host to be of clinical value. All three metals, arsenic, antimony, and bismuth, appear to be fatal to trypanosomes in concentrations of one in two hundred thousand or even less, but Cushny has shown that a concentration of arsenic of one in three thousand four hundred is necessary to kill the harmless non-parasitic protozoa, such as *Paramæcium* and *Colipidium*, while still stronger solutions of antimony and bismuth, namely $\frac{1}{970}$ and $\frac{1}{98}$ respectively, were necessary to effect the same result. These substances therefore appear to be true specifics against the trypanosomes, in the same way as quinine is a specific against the malaria organism.

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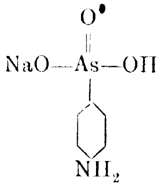
[1] Cushny, *loc. cit.*; Plimmer and Thomson, *Proc. Roy. Soc.*, B 80 (1908), 1477.

Some varieties of trypanosomes seem to be more sensitive to a given drug than others, and it therefore is desirable to use as many different specifics as possible in order that the parasites which resist one drug may be destroyed by another. It has also been established that the trypanosomes rapidly acquire a tolerance for these drugs, and therefore it is necessary to use large doses at the commencement of the treatment.

Arsenic Compounds.—As was stated above, it seems highly probable that atoxyl—



does not of itself exert a trypanocidal action, but that it gives rise to other substances which have this specific property. This problem has been the subject of extended investigations by Ehrlich and others,[1] but the question still remains to be definitely settled. Atoxyl was first thought to be an anilide of arsenic acid, C_6H_5—NH—$AsO(OH)_2$, but it was shown by Ehrlich and Bertheim to be a sodium salt of para-amino-phenyl-arsenic acid, NH_2—C_6H_4—$AsO(OH)_2$, an observation of very great importance, as it opened up the way for the preparation of a series of different compounds, by which means it was hoped to obtain compounds of a lower toxicity to the host (slightly organotropic) and a higher toxicity to the parasites (highly parasitotropic). For example, the amino-group may be acetylated, benzoylated, etc., or replaced by halogen, hydroxyl, or other groups by means of the diazo reaction, whilst by starting with substituted amines instead of aniline, derivatives can be prepared containing groups of the types —NHR and —NR_2, instead of NH_2. Of the derivatives thus obtained, some are $\frac{1}{20}$ and some 60 or 70 times as toxic as atoxyl. The entrance of a sulphonic acid group in the molecule yielded a substance the toxicity of which is of the same order as sodium chloride, but it is also quite inert towards the parasites.[1] This is in accordance with the general physiological inertia of the sulphonic acids The acetyl derivative—

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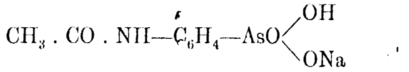
[1] A general account has been given by Ehrlich, *Ber.*, 42 (1909), 17-47.



$$CH_3 . CO . NH—C_6H_4—AsO\begin{matrix} /OH \\ \backslash ONa \end{matrix}$$

which is known as arsacetin, has certain marked advantages compared with atoxyl, being more stable and less toxic to some animals, while equally toxic to the parasites. Other acid groups have no advantage over acetyl, and with increasing length of the side chain the toxicity becomes far greater.

In order to make a decided advance, it is necessary to gain some idea of *how* atoxyl and its derivatives act in the animal body, as it would obviously be an advantage to use a substance as nearly as possible identical with the product of the metabolism of the body. It is found that arsenious oxide, certain triphenylmethane dyes, etc., can kill parasites in blood serum *in vitro*, but that atoxyl and its derivatives do *not*, though in the body they exert a trypanocidal effect in very high dilutions, such as $\frac{1}{1200000}$. This difference between action *in vitro* and *in vivo* may be explained by various different hypotheses, such as—

(1) Atoxyl may be decomposed in the body into aniline and arsenic acid, the effect on the parasites being due to the inorganic arsenic.

(2) According to Uhlenhuth and Woithe, atoxyl and compounds of a similar type may stimulate the cells to the production of derivatives (amboceptors) which kill the parasites.

(3) The body may produce new products of a synthetic type leading to the production of more active compounds.

The first of these hypotheses is the simplest, and is in accordance with many of the observed facts, but its probability is weakened by the fact that no arsenic acid is excreted, and preparations have been obtained which are from ten to twenty times as active as inorganic arsenic. We have no knowledge of any actual facts in support of the second theory, and with regard to the third, it seems probable that some new highly active compounds are produced, but Ehrlich considers that such products of metabolism are simpler than the original compounds, and are not very complex synthetic bodies.

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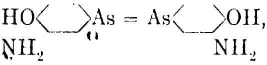
[1] See also Ehrlich, *loc. cit.*

Some significant facts have been brought to light which seem to indicate something of the nature of these metabolic changes. For example, there seems to be a close connection between the therapeutic efficiency of atoxyl and the resistance offered to it by the organism. Thus, a mouse which can readily tolerate $\frac{1}{150}$ is no better influenced therapeutically by *this* dose than is an average mouse which can only stand $\frac{1}{300}$ by *that* dose. One which was very sensitive and was poisoned by $\frac{1}{400}$, showed a very marked trypanocidal effect. This seems to indicate that the organism changes atoxyl into a more toxic substance, which also acts very strongly on the parasites. A change of this kind seems probably to be connected with the reduction of the arsenic from the pentavalent to the trivalent state.

Atoxyl, on reduction, gives *p*-aminophenyl-arsenious oxide, $NH_2\langle\quad\rangle AsO$, and with stronger reducing agents *p*-diaminoarsenobenzene, $NH_2\langle\quad\rangle As = As\langle\quad\rangle NH_2$. The reduction products of this type are generally more toxic and more active against trypanosomes than the corresponding derivatives containing pentavalent arsenic. The following table shows the dilutions at which one cubic centimetre will kill a mouse weighing twenty grams:—

Group in para position to Arsenic.	Form in which Arsenic is Present.		
	$R—\overset{\text{V}}{As}O\langle^{OH}_{ONa}$	$R—\overset{\text{III}}{As} = O$	$R—\overset{\text{III}}{As} = \overset{\text{III}}{As}—R$
$—NH_2$	1 : 200	1 : 15,000	1 : 6,000
$—OH$	1 : 75	1 : 13,000	1 : 1,000
$—NH—CH_2—COOH$	1 : 20	1 : 1,000	1 : 70

These reduction products show a *very marked* trypanocidal action, even *in vitro*. *p*-Hydroxy-phenyl-arsenious oxide, $HO\langle\quad\rangle As = O$, is the strongest, and in a dilution of one in ten million kills trypanosomes in one hour. When it is realized that atoxyl does not kill trypanosomes even in five per cent. solution, and that the hydroxy compound, $HO\langle\_\_\rangle AsO(OH)(ONa)$, does not do so in one or two per cent. solutions, it will be seen what an enormous change is produced by reduction. This is an example of the increased toxicity of unsaturated compounds (*e.g.* carbon monoxide, hydrocyanic acid, acrolëin, etc., *cf.* Chapter II.). The increased trypanocidal action *in vitro* is accompanied by an increased action *in vivo.* One cubic centimetre of a one in forty thousand solution of *p*-hydroxyphenyl-arsenious oxide caused the parasites to vanish from the blood of a mouse and for it to remain free for seven days. In the other members of the series, action *in vivo* is parallel to action *in vitro*, and therefore it indicates that the action of the derivatives of phenyl-arsinic acid is due to a reduction process, and indeed most of the evidence from all sides points to the probability of the trypanocidal action of arsenic and antimony being dependent on the presence of these elements in the trivalent state.

Some of these trivalent aromatic arsenic compounds are now extensively used in therapeutics. These are of the type $R—As = As—R$, rather than of the type $R—As = O$, and are distinguished by their comparatively low toxicity. The reduction product of atoxyl itself, $NH_2\langle\_\_\rangle As = As\langle\_\_\rangle NH_2$, has very high trypanocidal powers, but the compounds that have had the greatest success are dihydroxy-diamino-arsenobenzene,  $\underset{NH_2}{HO\langle\_\_\rangle} As = As\underset{NH_2}{\langle\_\_\rangle OH}$, and its derivatives, and the reduction product from phenylglycine-arsenic acid—

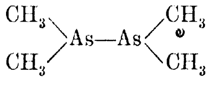
$$(HO)_2AsO\ .\ C_6H_4—NH—CH_2\ .\ COOH,$$

namely,

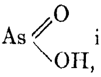
$$HOOC—CH_2—NH—\langle\_\_\rangle As = As\langle\_\_\rangle NH\ .\ CH_2—COOH.$$

These compounds will be discussed in the next section.

The aliphatic arsenic compounds are, at the present day, of no very great therapeutic importance. Cacodyl—

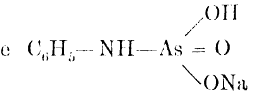


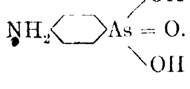
is poisonous, but the very soluble cacodylic acid, $(CH_3)_2 =$

 $As{=}O(OH)$, is comparatively harmless and inert. By reason of their excessive stability, its salts do not show a strong enough arsenical effect, and therefore do not find any therapeutic application. The same applies to "*new*"-*cacodyl* (*Arrhenal*), which is monomethyl-arsinic acid, $CH_3—AsO(OH)_2$, all these aliphatic compounds having been practically superseded by the aromatic.

An account of most of these aliphatic arsenic compounds, and of the earlier aromatic ones, is given by Martindale in a paper communicated to the International Congress of Applied Chemistry, London, 1909. Section VIII. B, p. 28.

Guaiacol cacodylate, $(CH_3)_2AsO . O . C_6H_4 . OCH_3, H_2O$, is known as *Cacodyliacol* (p. 167).

Aromatic Arsenic Compounds.—Atoxyl was the first aromatic arsenic compound to attain an extended use in therapeutics, and it is still the best known. By heating aniline arsenate, Béchamp[1] in 1863 obtained a substance which he took to be the anilide of arsenic acid, $C_6H_5—NH—AsO(OH)_2$, and described the sodium, potassium, barium, and silver salts. A sodium derivative of this substance was introduced into therapeutics under the name of *atoxyl*, and its correct empirical formula was established by Fourneau,[2] who attributed to it the structure  $C_6H_5—NH—As(OH)(=O)(ONa)$. It is, however, a neutral substance, and the sodium-free product obtained from it was found to be acid, and to be identical with the product obtained by Béchamp.[3] It seemed unlikely that this compound, $C_6H_8O_3NAs$, was really an anilide, and Ehrlich and Bertheim were able to show conclusively that it was para-amino-phenyl-arsinic acid, having the structure,



$NH_2C_6H_4As(OH)(=O)(OH).$

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[1] Béchamp, *C. R.*, 56 (1863), 1173.
[2] Fourneau, *Journ. Pharm. Chim.*, 6 Series, 25 (1907), 332.
[3] Ehrlich and Bertheim, *Ber.*, 40 (1907), 3292.

"The following were the chief reasons in support of this view:—

(1) Atoxyl cannot be hydrolyzed into arsenic acid and aniline by any of the ordinary agents used to hydrolyze anilides.

(2) It contains a primary amino group, which is easily diazotized and coupled with phenols and amines. It is readily acetylated, yielding a stable acetyl derivative.

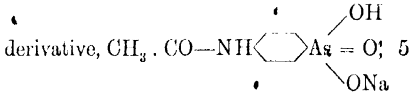
(3) Atoxyl corresponds in its properties with the arylarsonic acids of the type previously described by Michaelis and Reese.

(4) Hydriodic acid reacts with atoxyl, replacing the arsenic group by iodine with formation of para-iodo-aniline, $NH_2\langle\quad\rangle I$, thus proving that the arsenic and the amino group are in the para position to each other.

Atoxyl is prepared by heating arsenic acid with an excess of aniline at 180°-190°, or by heating aniline with aniline arsenate. The sodium salt is then obtained by extracting with sodium carbonate and recrystallizing. The acid is often known as arsanilic acid, and its sodium salt as sodium arsanilate, by analogy to sulphanilic acid, $NH_2\langle\quad\rangle SO_2-OH$.

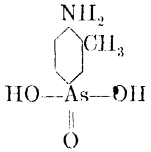
These terms, on account of their convenience, will hereafter be used to denote these compounds.

The sodium salt of this acid contains water of crystallization, the amount varying somewhat in the different commercial products. "*Soamin*" is the name given to a pure product of sodium arsanilate crystallized with five molecules of water. Other commercial products of this salt are known as *Arsamin*, *Atoxyl*, etc. These are used for the treatment of sleeping sickness, syphilis, and other diseases of protozoal origin, but unless they are used with caution, unpleasant and even dangerous by-effects, of which blindness is one of the worst, may arise.

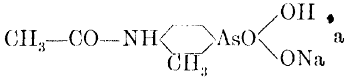
The acetyl derivative, 
$CH_3.CO-NH\langle\quad\rangle As{\overset{\diagup OH}{\underset{\diagdown ONa}{=O}}}, 5H_2O$, is said to be less toxic to many animals than atoxyl itself, and has the advantage of being more stable, so that its solutions can be sterilized by boiling. It is known as *Arsacetin* or *Acetyl-*

atoxyl, and the acid is readily prepared by the action of acetic anhydride on arsanilic acid. Arsacetin is then obtained by neutralizing with soda.

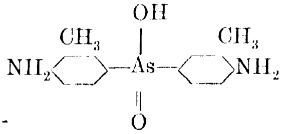
Ortho-toluidine yields derivatives exactly analogous to those obtained from aniline. For example, 2-amino-tolyl-5 arsinic acid—



is obtained by heating *o*-toluidine arsenate with twice its weight of *o*-toluidine at 180°-185°. The sodium salt is then obtained by treatment with sodium carbonate.[1]

The free acid can be acetylated, and the acetyl-compound yields a sodium salt,  $CH_3—CO—NH—C_6H_3(CH_3)—AsO(OH)(ONa)$ analogous to arsacetin, and known by the trade name of "*Orsudan.*" It is soluble in two and a half parts of water at body temperature, and resembles arsacetin in its action, being used in the same way for protozoal diseases.

Bis-2-amino-tolyl-5 arsinic acid—



is obtained as a by-product of the action of *o*-toluidine on *o*-toluidine arsenate, and it also yields the corresponding symmetrical diacetyl derivative by treatment with acetic anhydride.[2] In the same way, *bis-p*-aminophenyl-arsinic acid is obtained as a by-product in the preparation of arsanilic acid, and this compound also yields a diacetyl derivative. By the preparation of the following compounds :—

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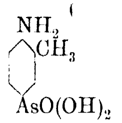
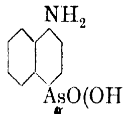
[1] Wellcome and Pyman, English Patent (1908), 855.

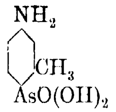
[2] Pyman and Reynolds, *J. C. S.*, 93 (1908), 1180.



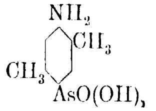
2-amino-tolyl-5 arsinic acid.



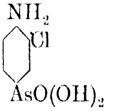
1-amino-naphthalene-4 arsinic acid.



3-amino-tolyl-6 arsinic acid.

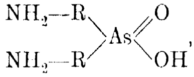


1-4-dimethyl-2-amino-phenyl-5 arsinic acid.



1-chloro-2-amino-phenyl-5 arsinic acid.

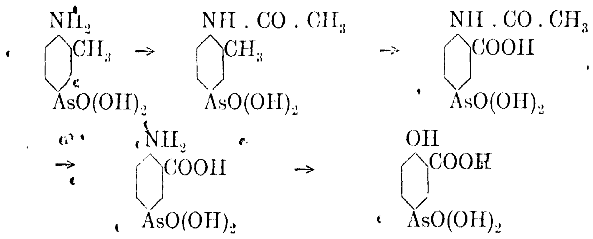
nda and Kahn[1] showed that the reaction of arsenic acid with aromatic amines is a general one, if the para position to the amino group is free. They also noticed the formation of arsinic acids of the type



$$\begin{matrix} NH_2-R \\ NH_2-R \end{matrix}\!\!>\!As\!\!<\!\!\begin{matrix} O \\ OH \end{matrix}$$

, as well as those of the ype $NH_2-R-AsO(OH)_2$, but this had not been noticed by Béchamp or by A. and R. Adler, who had just previously pre-ared 2-amino-tolyl-5 arsinic acid and 1-amino-naphthalene-4 arsinic acid.[2]

By acetylation and subsequent oxidation of the former they obtained acetyl-anthranil-arsinic acid, which by hydrolysis yields anthranil-arsinic acid, which was then converted into salicyl-arsinic acid by the diazo reaction.



Anthranil-arsinic acid.

Salicyl-arsinic acid.

Para-hydroxy-phenyl arsinic acid, $HO\left\langle\quad\right\rangle AsO(OH)_2$, is obtained from arsanilic acid by the diazo reaction,[1] and it has also been obtained by the action of phenol on arsenic acid at 150°, and the homologues of this acid may be obtained in a similar manner from ortho or meta cresol, or by the diazotization of the corresponding amino-acids.[2] As obtained from phenol it is a syrup, and it can be purified by recrystallization of its sodium salt.[3] Para-hydroxy-phenyl arsinic acid is not used therapeutically, but is the starting-point for the production of some very important derivatives.

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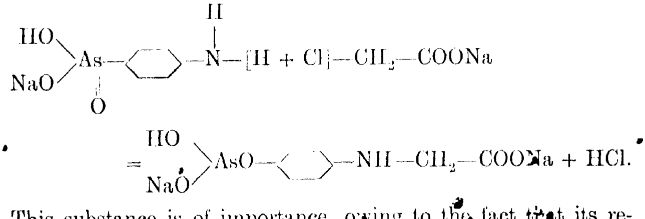
[1] Benda and Kahn, *Ber.*, **41** (1908), 1672.

[2] A. and R. Adler, *Ber.*, **41** (1908), 931.

The arsinic acids of the type $R_2N\langle\quad\rangle{-}AsO(OH)_2$ and $RHN\langle\quad\rangle{-}AsO(OH)_2$ do not appear to have found any therapeutic application. Para-dimethyl-amino-phenyl arsinic acid, $(CH_3)_2N \,.\, C_6H_4 \,.\, AsO(OH)_2$, is obtained by the action of arsinic trichloride on dimethylaniline, whereby $(CH_3)_2N \,.\, C_6H_4 \,.\, AsCl_2$ is formed, which is hydrolyzed, yielding the acid $(CH_3)_2N \,.\, C_6H_4{-}{-}As(OH)_2$, which gives the arsinic acid by oxidation with hydrogen peroxide.[4] It is also formed by the action of dimethyl sulphate on an alkaline solution of arsanilic acid.

An important derivative of arsanilic acid is phenylglycine-para arsinic acid, which is obtained by mixing solutions of sodium arsanilate with chloroacetic acid in hot aqueous solution—[5]



$$\begin{matrix}HO\\NaO\end{matrix}\!>\!\underset{\underset{O}{\|}}{As}-\langle\quad\rangle-\overset{\overset{H}{|}}{N}-[H + Cl]-CH_2-COONa$$

$$= \begin{matrix}HO\\NaO\end{matrix}\!>\!AsO-\langle\quad\rangle-NH-CH_2-COONa + HCl.$$

This substance is of importance, owing to the fact that its reduction product containing the arsenic in the trivalent condition is of great therapeutic value. This and other derivatives containing trivalent arsenic will be considered in the following section.

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[1] Barrowcliff, Pyman, and Remfry, *J. C. S.*, **93** (1908), 1893; Bertheim, *Ber.*, **41** (1908), 1853.

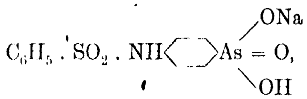
[2] D. R. P., 205,616.

[3] E. P., 6322 (1915).

[4] Michaelis, *Ber.*, **41** (1908), 1514; D. R. P., 200,605.

[5] *Ibid.*, 204,664.

The benzene-sulphonyl derivative of atoxyl,



is known as "*Hectine*," and has been successfully used in the local treatment of syphilis.[1]

A compound of arsanilic acid with allyl-thiourea (*cf.* p. 239) has been prepared, and is said to have valuable therapeutic properties and low toxicity.[2]

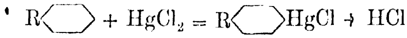
The arsinic acids and their derivatives described in the preceding pages are mostly prepared by the action of arsenic acid on a primary amine or a phenol, and this is the simplest method in those cases where it is applicable. A more general method of preparing arsinic acids has, however, been devised by Bart.[3] It consists in diazotizing a primary amine, and treating the diazo solution with a metallic arsenite, and warming the product whereby nitrogen is evolved and the salt of the arsinic acid formed.

$$\begin{aligned} &R.NH_2 \rightarrow R.N_2X \\ &R.N_2X + As(OM)_3 = R.N_2AsO(OM)_2 + MX \\ &R.N_2AsO(OM)_2 \rightarrow R.AsO(OM)_2 + N_2. \end{aligned}$$

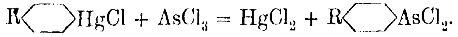
By a suitable choice of the radicle represented by R, practically any aromatic arsinic acid can be prepared.

Another widely applicable method of attaching arsenic to the aromatic nucleus is through the mercury compounds.[4]

Mercuric chloride readily reacts with many aromatic compounds, giving para-substituted mercury compounds:—



On treatment with arsenic trichloride, the mercury is replaced by arsenic:—



The dichlorarsines so obtained are easily converted into arsinic acids by hydrolysis and oxidation.

Trivalent Arsenic Compounds (Derivatives of Arsenobenzene).—The therapeutically valuable trivalent aromatic arsenic compounds are all of them obtained by reduction of the corresponding compounds containing pentavalent arsenic. Reducing agents convert arsanilic acid[1] into para-amino-phenyl arsenious oxide, NH_2–⬡–AsO, or into diaminodi-hydroxy-arsenobenzene, NH_2⬡As(OH)—As(OH)⬡NH_2, or into para-diamino-arseno benzene,

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[1] *Lancet*, 25 June, 1915.

[2] D. R. P., 294,632.

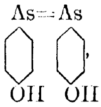
[3] *Ibid.*, 250,264.

[4] Roeder and Blasi, *Ber.*, 47 (1914), 2748.

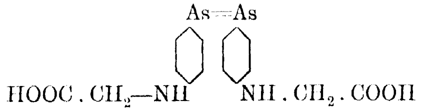
NH_2⬡As = As⬡NH_2.

The first is produced by weak reducing agents such as hydriodic acid, or sulphurous acid, the second by sodium amalgam and methy alcohol, and the third by stronger reducing agents, such as sodium hydrosulphite, etc.

Still stronger reducing agents, such as zinc and hydrochloric acid, reduce it to para-aminophenyl arsine, NH_2⬡AsH_2.

Arsenophenol, 

, is obtained by the reduction of para-hydroxyphenyl arsinic acid with a solution of sodium hydrosulphite, caustic soda, and magnesium chloride.[2] The sodium derivative of this substance is soluble in water, from solutions in which it is precipitated by alcohol. Phenylglycine arsinic acid when reduced in this way gives arseno-phenylglycine—



a reddish-brown powder, soluble in aqueous sodium carbonate.[3]

Very favourable results are said to have been obtained with this substance in the treatment of trypanosomiasis in rats, but it is not so well tolerated by larger animals, such as the horse or the donkey.[4] Favourable results are also said to have attended its use in syphilis, and it is claimed that in all cases it is free from the danger of harmful effects on the eyes.

In recent years another derivative of arsenobenzene intr duced by Ehrlich has been widely and successfully used in the treatment of syphilis.

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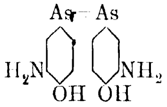
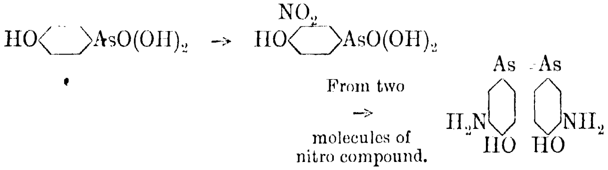
[1] M. L. B., English Patent, 17,619 of 1907; D. R. P., 206,057.
[2] *Ibid.*, 206,456.   [3] *Ibid.*, 206,057.
[4] Breinl and Nierenstein, *Zeitschr. f. Immunitätsforsch.* (1909), 169.

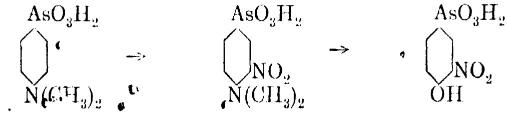
This preparation is dihydroxy-diamino-arsenobenzene—



better known as "**606**" or *Salvarsan*. It is prepared from *p*-hydroxy-phenyl arsinic acid, $HO\langle\quad\rangle AsO(OH)_2$, which on treatment with nitric and sulphuric acids yields a mono-nitro compound, the nitro group entering into the ortho position to the hydroxyl and meta to the arsinic group. This compound, on reduction with caustic soda, sodium hydrosulphite, and magnesium chloride, gives dihydroxy-diamino-arsenobenzene—[1]



An alternative method of preparing 3-nitro-4-hydroxyphenyl arsinic acid starts from *p*-dimethylaminophenyl arsinic acid, prepared as described on p. 207. This on nitration gives 3-nitro-4-dimethylaminophenyl arsinic acid, which on treatment with alkali gives 3-nitro-4-hydroxyphenyl arsinic acid.[2]



In addition to the method already given, this can be reduced to dihydroxy-diamino-arsenobenzene by treating it with zinc and acetic acid at 25°-30°, and then with hydrochloric acid and sulphurous acid at 50°-60°. The addition of the sulphurous acid appears to prevent the reduction from going beyond the "arseno" stage.[3]

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[1] D. R. P., 224,953.

[2] E. P., 22,521 (1914).

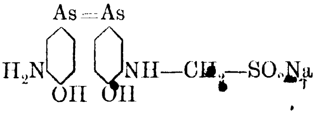
[3] *Ibid.*, 21,421 (1914).

Dihydroxy-diamino-arsenobenzene is obtainable as the hydrochloride under the trade names of *Salvarsan*, *Kharsivan*, and *Arsenobenzol*, but before use it is generally[1] transformed into the sodium salt by adding the correct amount of caustic soda solution to its aqueous solution. Great care has to be taken in making up these solutions, which do not keep well, so that they have to be prepared immediately before use. They are administered either by intravenous or intramuscular injection.

Splendid results have been obtained with this compound, especially when used in conjunction with mercury, though some of the more extravagant claims, as for example, that syphilis could be cured by a single injection, have not been substantiated.

Although its toxicity is low, it is by no means negligible, and fatal results have sometimes attended its use, but in the majority of cases these can be attributed to faulty technique or to its use in cases where the condition of the patient was already very bad. Its action on spirochaetes *in vitro* is very weak, and it was therefore presumed that it underwent some change in the organism with the formation of more active products. According to a recent investigation,[2] these changes are very complex, a large number of different compounds being formed.

To overcome the drawbacks due to the laborious technique of administering Salvarsan, a derivative soluble in water was soon afterwards introduced. This substance is known as *Neosalvarsan*, *Neokharsivan*, *Novarsenobenzol*, etc., and has the structure represented by the formula :—



It is prepared[3] by adding an aqueous solution of formaldehyde sulphoxylate to an aqueous solution of Salvarsan. A precipitate is formed which redissolves in sodium carbonate solution to form a clear yellow solution of Neosalvarsan.

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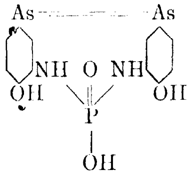
[1] The hydrochloride itself, in aqueous solutions or oily suspensions, has also been used for injection.

[2] Sieburg, *Zeit. physiol. Chem.*, 97 (1916), 53–108.

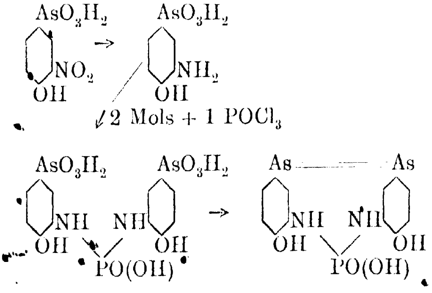
[3] D. R. P. 245,756.

Not only does Neosalvarsan possess the advantage of ready solubility in water and in saline solutions, giving neutral solutions, but it is also said to be better tolerated by patients than is Salvarsan itself. It is administered by intravenous or intramuscular injection, and its therapeutic properties are similar to those of Salvarsan.

Another derivative of Salvarsan which has recently attracted a good deal of favourable attention is *Galyl*, a substance having the composition shown by the formula :—



It is prepared as follows: 3-nitro-4-hydroxyphenyl arsinic acid is electrolytically reduced to 3-amino-4-hydroxyphenyl arsinic acid.[1] This is then treated with phosphorus oxychloride in presence of caustic soda solution, and the product reduced with sodium hydrosulphite.[2]



t is used in the form of its sodium salt which is readily soluble n water, yielding solutions suitable for intravenous injection. ts solution in a dilute solution of glucose is also used for intra-uscular injection.

Considerable attention has been paid recently to the metallic ompounds of Salvarsan. These are of the "additive" type, and are formed by virtue of the residual affinity of the "arseno," —As = As— group.[1] A compound of one molecule of Salvarsan with one molecule of cupric chloride is said to be remarkably effective against sleeping sickness. The preparation is described of copper and of silver compounds, by mixing a solution of Salvarsan with a copper or a silver salt, and precipitating the mixture with a solution of caustic soda.[2]

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[1] E. P., [illegible]087 (1915).

[2] *Ibid.*, 9234 (1915).

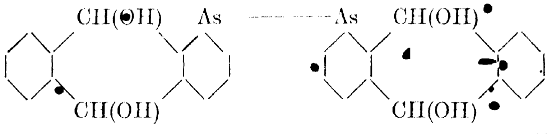
"Sodium Salvarsan" is prepared by precipitating a solution of Salvarsan in caustic soda with alcohol, in the presence of a substance capable of stabilizing the product.[3] It is said to be useful in the treatment of syphilis.[4]

Various other metallic derivatives and their methods of preparation have since been described.[5] One of these is known as "*Luargol*," and is a compound of Salvarsan with silver bromide and antimony. It appears to have the composition[6] $(C_{12}H_{12}O_2N_2As_2)_2$, AgBr, $SbO(H_2SO_4)_2$, and is said to be stable and to be less toxic and more effective therapeutically than the parent substance.[7]

In addition to the derivatives of Salvarsan, various more complex derivatives of arsenobenzene have been prepared and investigated. For example, 3-4-5-3′-4′-5′-hexamino-arsenobenzene is said to be a powerful spirillocide.[8]

Resorcinol readily reacts with arsenic acid giving 2-4-dihydroxyphenyl arsinic acid, from which a series of derivatives of arsenobenzene have been obtained by reduction.[9]

From α-aminoanthraquinone, the corresponding arsinic acid has been prepared by Bart's reaction (p. 208). This on reduction with sodium hydrosulphite gives 1-1′-arsenoanthranol:—



which is readily oxidized by air to anthraquinone-1-arsenoxide:—

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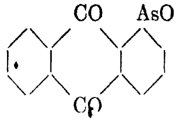
[1] Ehrlich and Karrer, *Ber.*, **48** (1915), 1634.
[2] E. P., 1247 (1914). [3] *Ibid.*, 15,931 (1912), 24,152 (1914).
Münchener med. W. (1915), 177.
Danysz, E. P., 104,496; 104,497 (1916).
Danysz, *C. R.*, **159** (1914), 452.
C. *R.*, **161** (1915), 685, **162** (1916), 440.
D. R. P., 286,854, 286,855. [9] Bauer, *Ber.*, **48** (1915), 509.



These compounds are toxic, and they are easily decomposed into anthraquinone and arsenic acid.[1]

A very large number of other derivatives of phenylarsinic acid and of arsenobenzene have been described, the above-mentioned having been given as typical examples.

In addition to the symmetrical derivatives of arsenobenzene, R—As = As—R, already mentioned, mixed or unsymmetrical derivatives of the type R—As = As—R′ can be obtained by the reduction of an equimolecular mixture of arsinic acids, $RAsO_3H_2$ and $R'AsO_3H_2$.[2] Another method of obtaining unsymmetrical arsenobenzenes is as follows: The arsinic acid is first reduced to the corresponding arsine by means of metal and mineral acid,[3]

$$R . AsO_3H_2 \rightarrow R . AsH_2,$$

and this can then be condensed with aryl arsenoxides or halides.

$$R . AsH_2 + OAsR' = R . As = As . R' + H_2O.^4$$

This method is also applicable to the production of mixed arseno-stibino, and arseno-bismutho compounds[5] (*cf.* p. 215):—

$$R . AsH_2 + R'SbCl_2 = R . As = Sb . R' + 2HCl.$$

As can be seen from the preparation of Salvarsan, the use of sodium hydrosulphite is not applicable to the formation of arseno compounds containing a nitro group as this is also reduced by the hydrosulphite. It has been found, however, that hypophosphorus acid is a specific agent for reducing the arsinic acid group to the arseno group, and by this means arsinic acids containing a nitro group or an azo group can be reduced to the corresponding arseno compounds.[6]

Organic Antimony Compounds.—The trypanocidal action of antimony, compared with that of arsenic, has been discussed in the first section of this chapter. Unfortunately, the aromatic antimony compounds compare unfavourably with those of arsenic with regard both to ease of preparation and stability. For example, *p*-aminophenyl-stibinic acid, the antimony analogue of arsanilic acid, cannot be obtained by the interaction of antimony pentoxide and aniline, and the statement[1] that it has been obtained from aniline and antimony trichloride by a method analogous to Michaelis's synthesis of *p*-dimethylaminophenyl arsinic acid (p. 207) is quite incorrect.

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[1] Benda, *Journ. prakt. Chem.*, **95** (1917), 74.

[2] D. R. P., 251,104, 270,254.

[3] *Ibid.*, 251,751.

[4] *Ibid.*, 251,511.

[5] *Ibid.*, 254,187, 269,699, 269,743, 269,744, 269,745.

[6] Karrer, *Ber.*, **47** (1914), 2275; D. R. P., 271,271.

Aryl-stibinic acids can, however, be obtained by the action of sodium antimonite on diazo solutions[2] in a way somewhat analogous to Bart's reaction (p. 208), and *p*-aminophenylstibinic acid has been prepared by this method, but the preparation is difficult and the yields are low. The compound moreover is amorphous and difficult to purify. Aryl-stibinic acids can also be obtained by the action of alkali[3] on compounds obtained from antimony trichloride and diazo compounds.[4]

Aryl-stibinic acids can be nitrated in the usual way,[5] and *p*-chlorophenyl-stibinic acid on nitration gives 3-nitro-4-chlorophenyl-stibinic acid, which, on boiling with alkali, gives 3-nitro-4-hydroxyphenyl-stibinic acid. This, on reduction with sodium hydrosulphite, gives 3-3′-diamino-4-4′-dihydroxy-stibinobenzene, he antimony analogue of Salvarsan.[6]

A large number of other aromatic antimony compounds, and mixed arseno-stibino compounds have been prepared[7] (*cf.* p. 214).

None of the compounds which have been tried up to the present fulfil all the conditions necessary for a really efficient rypanocide. These conditions may be summed up as follows:—[8]

(1) The compound must be non-irritant, and capable of remaining in perfect solution at the temperature and alkalinity of the tissues.

(2) It must act quickly on the trypanosomes before they can acquire a tolerance to the drug.

(3) When the trypanosomes have been expelled from the blood by a single full therapeutic dose, there must be no recurrence in the majority of cases within some fixed time, which will

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[1] Breinl and Nierenstein, *Annals of Tropical Medicine*, 2 (1909).

[2] D. R. P., 254,421.

[3] *Ibid.*, 261,825.

[4] P. May, *J. C. S.*, 101 (1912), 1037.

[5] *Ibid.*, 1033.

[6] D. R. P., 268,451.

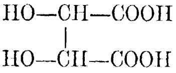
[7] *Ibid.*, 259,875, 269,205, 267,083, 254,187, 269,699, 269,743, 269,744.

[8] Thomson and Cushny, *Proc. Roy. Soc.*, 82 B (1910), 249.

depend to some extent on the particular host experimented with, and on the strain of parasites used.

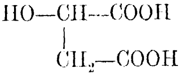
Although the arsenic compounds which have been described do not fulfil the second and third of these conditions, yet the majority of them fulfil the first of these quite admirably, but in the case of antimony difficulty has been experienced in obtaining derivatives to fulfil even this condition.

Of the various compounds which have been tried therapeutically, those of a similar nature to ordinary tartar emetic (potassium antimonyl-tartrate) are amongst those giving the best results. Thomson and Cushny,[1] have experimented with many compounds of this type derived from various hydroxy acids, and the best results were obtained with compounds prepared from tartaric and malic acids:—



$$\begin{array}{c}\text{HO—CH—COOH}\\ |\\ \text{HO—CH—COOH}\end{array}$$

Tartaric Acid.



$$\begin{array}{c}\text{HO—CH—COOH}\\ |\\ \text{CH}_2\text{—COOH}\end{array}$$

Malic Acid.

The sodium and potassium antimonyl-tartrates seemed to be very nearly equal in their efficiency, but the ethyl ester of antimonyl-tartaric acid appeared to have some advantage over these alkali salts. Potassium ammonium antimonyl-tartrate is known as *Antiluetin.*

Good results are also claimed for certain antimony derivatives of thioglycollic acid.[2]

The injection of finely divided metallic antimony has also been advocated as the most satisfactory treatment of trypanosomiasis.[3]

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[1] Thomson and Cushny, *Proc. Roy. Soc.*, **82 B** (1910), 249.

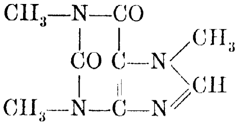
[2] Rowntree and Able, *The Journal of Pharmacology* (Baltimore), **2**, (1910), 101-144.

[3] Plimmer and Fry, *Proc. Roy. Soc.*, **81 B** (1909), 334. Plimmer, Fry, and Ranken, *Proc. Roy. Soc.*, **83 B** (1910), 140.

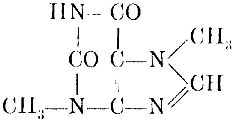
CHAPTER XV.

PURINE DERIVATIVES (DIURETICS) AND OTHER URIC ACI ELIMINANTS.

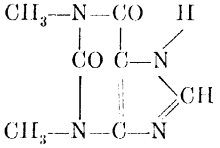
CAFFEINE, the best-known drug of the purine group, is used a a cardiac tonic and cerebral excitant, but in addition it has diuretic action, as also have other members of the purine grou Caffeine sodium cinnamate is known as *Hetol*.



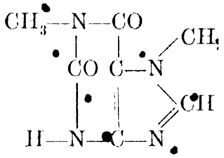
Caffeine.



Theobromine.



Theophylline.



Paraxanthine.

Although the action of theobromine on the nervous system is far weaker than that of caffeine, its diuretic action is as strong Both substances suffer from the disadvantage of sparing solubility and small power of resorption. To overcome the drawback of slight solubility, double salts of the sodium derivatives of caffeine and theobromine, with sodium salicylate, benzoate and acetate, have been prepared. Compounds of sodium theobromine with sodium salicylate and acetate are known as *Diuretin* and *Agurin* respectively. The acyl-amino derivatives of caffeine are said to have a strong diuretic action without the by-effects of caffeine. Monoacetyl-amino-caffeine, diacetyl amino-caffeine, etc., have been prepared [1]

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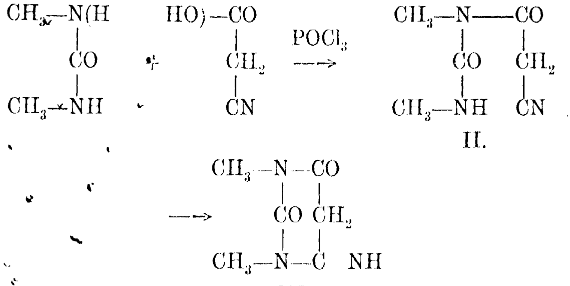
[1] D. R. P., 139,960.

According to the investigations of Ach,[1] the dimethylxanthines have a stronger diuretic action than trimethylxanthine (caffeine). Of these, theobromine (3-7 dimethyl) has the weakest, and theophylline (1-3 dimethyl) the strongest action, but that of paraxanthine (1-7 dimethyl) is the most persistent. *Theophylline*, which differs from caffeine in having less action on the heart, has been introduced into therapeutics under the name of *Theocine*, in the form of its compound with sodium acetate. Its practical application is due to a synthetic process, as the natural alkaloid is far too expensive.

Theophylline has been synthesized by Fischer and by Traube,[2] the technical preparation being based on the latter method.[3]

The synthesis of theophylline was carried out by Traube according to the following method. Dimethyl urea was first condensed with cyanacetic acid by means of $POCl_3$, and the resulting compound (II.) converted into the cyclic base (III.) by the action of alkali. This base, when treated with sodium nitrite and acetic acid, yields the isonitroso compound (IV.)

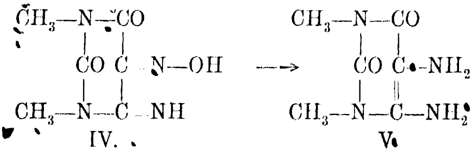


$$\begin{array}{c} CH_3-N(H \\ | \\ CO \\ | \\ CH_3-NH \end{array} + \begin{array}{c} HO)-CO \\ | \\ CH_2 \\ | \\ CN \end{array} \xrightarrow{POCl_3} \begin{array}{cc} CH_3-N & -CO \\ | & | \\ CO & CH_2 \\ | & | \\ CH_3-NH & CN \end{array}$$

II.

$$\longrightarrow \begin{array}{cc} CH_3-N- & CO \\ | & | \\ CO & CH_2 \\ | & | \\ CH_3-N- & C \quad NH \end{array}$$

III.



$$\begin{array}{cc} CH_3-N- & CO \\ | & | \\ CO & C \quad N-OH \\ | & | \\ CH_3-N- & C \quad NH \end{array} \longrightarrow \begin{array}{cc} CH_3-N- & CO \\ | & | \\ CO & C-NH_2 \\ | & \| \\ CH_3-N- & C-NH_2 \end{array}$$

IV. V.

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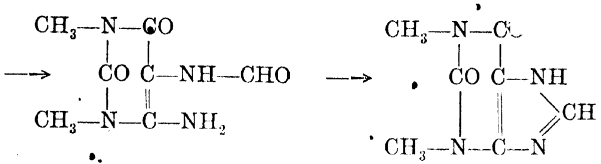
[1] Ach, *A. e. P. P.*, 44 (1900), 319.

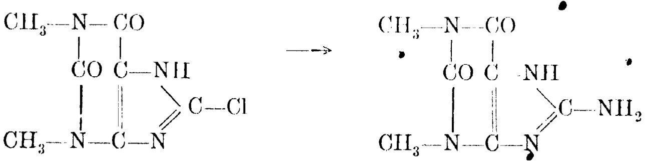
[2] W. Traube, *Ber.*, 33 (1900), 3053.



VI. VII.

which is reduced to the corresponding amine (V.) by means of ammonium sulphide. This amine is then converted, by formic acid, into its formyl derivative (VI.), which loses H_2O and yields theophylline (VII.) when heated with alkali.

8-Amino-theophylline is obtained by the action ammonia on 8-chloro-theophylline,[1] and has strong diuretic action. 8-Amino-paraxanthine and its alkyl derivatives have been obtained in a similar manner.[2]



3-Monomethyl-xanthine has an appreciable diuretic action, but in 7-monomethyl-xanthine it is vanishingly small. The diuretic action of xanthine itself is extremely small, and that of *iso*-caffeine (1-7-9 trimethyl-xanthine) is also very weak.

Uric Acid Solvents, etc.—In addition to the diuretics, the various compounds that have been advocated as remedies for gout may be divided into two classes—those which are designed to diminish the formation of uric acid in the body, and those which are intended to act as solvents for the uric acid after it has been formed. Of the latter class it may be said that many substances have been obtained, such as piperazine and urotropine, which are capable of dissolving uric acid *in vitro*, but are probably quite incapable of dissolving it in the highest possible concentrations that can be present in the body. Naturally many compounds have been prepared which are intended to combine both functions.

For example, quinic acid, $C_6H_7(OH)_4 . COOH$, which exists in cinchona bark and coffee beans, is said to diminish the formation of uric acid,[1] and its lithium and piperazine salts have been introduced under the names of *Urosin* and *Sidonal* respectively. In these cases the lithium or piperazine is intended to act as a uric acid solvent.

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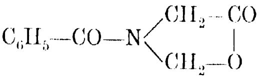
[1] D. R. P., 156,900. [2] *Ibid.*, 156,901.

It has also been noticed that the presence of organic acids in the organism generally decreases the amount of uric acid formed, and that this effect is greater in proportion to the number of carbon atoms present in the acid. For this reason the use of diphenyl tartrate has been suggested, $(-CH(OH)-COOC_6H_5)_2$, and salicylic acid has also been used, especially in the form of a condensation product of saligenin and tannic acid. A salicylate of urea has been recommended under the name of *Ursal*. Other compounds used for this purpose are hippuric acid, methylene-hippuric acid—



and its meta-nitro compound.[2]

Drugs of the second class, namely those the function of which is to prevent the *deposition* of uric acid rather than to prevent its *formation*, are more numerous. The alkaline carbonates have been widely used for this purpose, and especially lithium carbonate, as it has been found that the lithium salt is by far the most soluble of all the inorganic salts of uric acid. The alkaline tartrates, citrates, etc., are also used as well as the carbonates. The bad effects of lithium on the nervous system have led to the introduction of various organic bases which form even more soluble salts with uric acid.

The employment of lithium and these bases as uric acid solvents is fallacious, because there is always sufficient sodium present in the body to form the sparingly soluble sodium urate, and a double decomposition between salts takes place with the formation of the least soluble. If we designate sodium urate for the sake of simplicity as NaU, then an equation such as $LiU + NaCl \rightleftarrows NaU + LiCl$, will run from left to right under the conditions present in the organism. Nevertheless, some considerable benefit is often derived from these remedies, although it may not be due to their solvent action on the uric acid.

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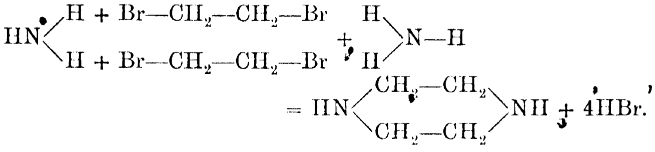
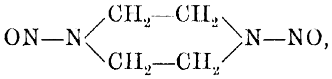
[1] Weiss, *Berl. klin. W.*, 14 (1899).

[2] D. R. P., 148,669.

Of the various organic bases that have been used as substitutes for lithium, piperazine is the most important. It was obtained by Hofmann by the action of ammonia on ethylene dichloride or dibromide.[1]



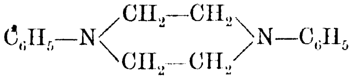
It is most readily purified by treating the reaction mixture with nitrous acid, whereby nitroso-piperazine—



is obtained, from which piperazine can be regenerated by the action of hydrochloric acid or reducing agents.[2]

Many different modifications of this synthesis have been devised,[3] but only one of them calls for mention. By the action of aniline on ethylene dibromide, diethylenediphenyldiamine is obtained,[4] which yields a nitroso compound on treatment with nitrous acid. It has been shown[5] that this on treatment with alkalies yields piperazine and nitroso-phenol.

Aniline with ethylene dibromide gives—



just as ammonia gives piperazine.

This with nitrous acid yields—

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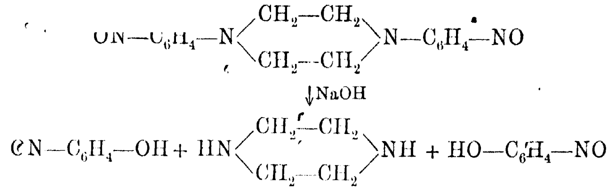
[1] Hofmann, *Proc. Roy. Soc.*, 10 (1860), 231; *Ber.*, 23 (1890), 3297.

[2] D. R. P., 59,222.

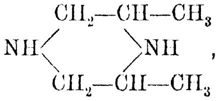
[3] *Ibid.*, 60,547, 63,618, 66,461, 65,347, 70,055, 71,576, 83,524, 70,056, 73,125, 67,811, 73,354, 74,628, 98,031, 100,232. See Friedländer, *Fortschr.*, III. 948, IV. 1201.

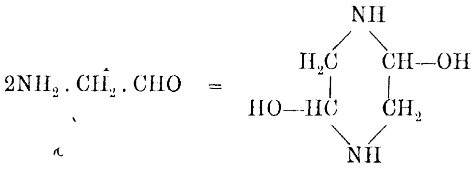
[4] Hofmann, *Proc. Roy. Soc.*, 9 (1858), 277.

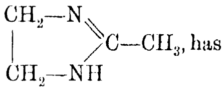
[5] Bischler, *Ber.*, 24 (1891), 717; and D. R. P., 60,547, etc.

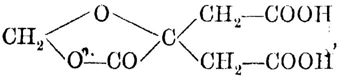


Piperazine is also known under the name of Dispermin, and its salt with quinic acid (p. 220) is used under the names of *Urol* and *Sidonal.*

The tartrate of dimethyl-piperazine,  is known as *Lysetol,* and has the advantage of being non-poisonous and non-hygroscopic. Dihydroxy-piperazine has also been investigated, and it resembles piperazine in its properties of a uric acid solvent. It is obtained by polymerizing aminoacetaldehyde with cold hydrobromic acid.[1]



An ethylene-ethenyl-diamine,  has been prepared[2] by heating ethylene diamine hydrochloride with sodium acetate and introduced under the name of *Lysidin.* It is said to be eight times as strong as piperazine in its solvent action on uric acid *in vitro.*[3] Similar propenyl and butenyl derivatives have been prepared.[4]

Urotropin (hexamethylene-tetramine), *cf.* Chapter XI., has been recommended as a uric acid solvent, its salts with quinic acid being known as *Quinotropin*, and its salicyl derivatives as *Saliformin*. *Helmitol*, or *New-urotropin*, is the anhydro-methylene-citrate of hexamethylene-tetramine. The acid, , is obtained by heating citric acid with paraformaldehyde, or in better yield by the action of chlor-methyl alcohol, Cl . CH_2—OH, on citric acid at 130°-140° C.[1]

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[1] E. Fischer, *Ber.*, 27 (1894), 169.

[2] Ladenburg, *Ber.*, 27 (1894), 2952; D. R. P., 78,0[illegible].

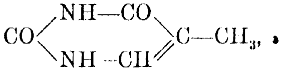
[3] *Deut. med. W.*, 1 (1894).

[4] Klingenstein, *Ber.*, 28 (1895), 1173, 1068.

The sodium salt of the acid has also been used by itself as a uric acid solvent, under the name of *Citarin*.

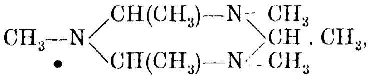
According to Tunnicliffe and Rosenheim, the solubility of uric acid in blood serum is raised by the presence of piperidine, and they suggested the use of piperidine tartrate.[2]

A substance of unknown composition which is used a good deal as a uric acid solvent is thyminic acid, a complex substance prepared by a lengthy process from the thymus gland.[3] It is also known by the trade name of *Solurol*. On boiling with aqueous sulphuric acid, it breaks down into Thymin,



which shows that it is chemically related to piperazine, lysidine, etc.

Various other cyclic bases of this type, such as,



also have a strong solvent action on uric acid.[4]

Certain quinoline derivatives have been found useful in the treatment of gout, sciatica, etc., as they have analgesic properties in addition to being uric acid eliminants and urinary antiseptics. The simplest of these is *Atophan*, or 2-phenyl-quinoline-4 carboxylic acid,

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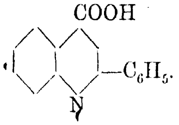
[1] D. R. P., 129,255, 150,949.

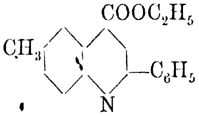
[2] *Lancet* (1889), 189.

[3] D. R. P., 104,908.

[4] Unpublished observations of the author.



Its ethyl ester is known as *Acitrin*, and the methyl derivative of this,

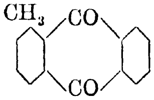


is known as *Novatophan*.

CHAPTER XVI.

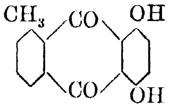
PURGATIVES AND OTHER SUBSTANCES ACTING ON THE GASTRO-INTESTINAL TRACT.

Anthraquinone Derivatives.—Many aperient drugs, such as cascara, rheum (rhubarb), senna, and aloe, contain hydroxyl derivatives of methyl-anthraquinone. The position of the methyl group in these substances is not quite certain, but it is probable that most of them are derivatives of *a*-methyl-anthraquinone,



These substances are very valuable as purgatives, owing to the fact that they have but little effect on the stomach and do not cause inflammation of the intestine. On the other hand, some of the drug is absorbed from the intestine into the system, and is liable to have an undesirable action on the kidneys. This effect is usually very slight, however.

Chrysophanic acid, dihydroxy-methyl-anthraquinone—[1]



is one of the milder of the natural purgatives of this group, and is present in rhubarb and many other purgative drugs, usually as a glucoside, *chrysophan*. The number and position of the hydroxyl groups has a powerful influence on the physiological action of the substance. For example, *emodin*, trihydroxy-methyl-anthraquinone, $C_{15}H_{10}O_5$, probably having the constitution—[2]

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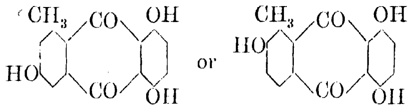
[1] Jowett and Potter, *J. C. S.*, 83 (1903), 1327.

[2] Hesse, *Annalen*, 309 (1899), [illegible]2.



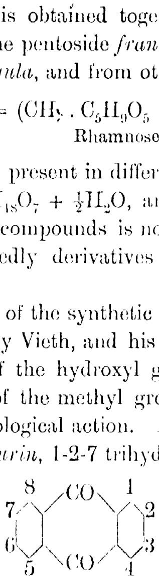
has a considerably more powerful action than chrysophanic acid. This substance is obtained together with rhamnose by the decomposition of the pentoside *frangulin*, obtained from the bark of *Rhamnus frangula*, and from other similar sources.

$$C_{21}H_{20}O_9 + 2H_2O = (CH_3 . C_5H_9O_5 + H_2O) + C_{15}H_{10}O_5.$$

Rhamnose. Emodin.

The active principles present in different varieties of aloes are known as aloïn, $C_{17}H_{18}O_7 + \frac{1}{2}H_2O$, and barbaloïn, $C_{16}H_{18}O_7$. The structure of these compounds is not known with certainty, but they are undoubtedly derivatives of polyhydroxy-anthraquinones.

The purgative action of the synthetic hydroxy-anthraquinones has been investigated by Vieth, and his results indicate that the number and position of the hydroxyl groups is of importance, but that the presence of the methyl group seems to have little influence on the physiological action. He found that the most active was *anthrapurpurin*, 1-2-7 trihydroxy-anthraquinone—



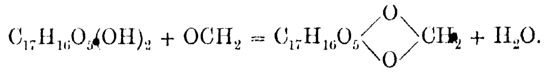
Substance.		Strength of Action.
Anthrapurpurin,	1-2-7 trihydroxy-anthraquinone .	1
Flavopurpurin,	1-2-6 ,, ,, .	$\frac{1}{2}$
Anthragallol,	1-2-3 ,, ,, .	$\frac{1}{3}$
Purpuroxanthin,	1-3 dihydroxy- ,, .	$\frac{1}{6}$
Alizarine-Bordeaux,	1-2-3-4 tetrahydroxy- ,, .	$\frac{1}{10}$
Purpurin,	1-2-4 trihydroxy- ,, .	$\frac{1}{20}$

A number of compounds, such as alizarin (1-2 dihydroxy-anthraquinone), rufigallic acid (hexa-hydroxyanthraquinone), etc., are inactive. Some of the active compounds contain a methyl group, and others do not.

An important factor in determining the purgative action is the length of time that the substance remains in the intestine, for when it is absorbed it can no longer exert a purgative action.[1] The superiority of the glucosides and acetyl derivatives over the parent substances, and of the natural drugs over the synthetic, is due to the slower absorption of the former. Chrysophanic acid when quite pure is no longer a purgative, owing to its rapid absorption.[2] Rapid absorption also increases the risk of undesirable effects on the kidneys, and therefore it is to be avoided on this account also. For these reasons, synthetic substances such as anthrapurpurin are inferior to the natural compounds, but synthetic substances of a more complex nature which are slowly absorbed have also been obtained.

Anthrapurpurin diacetate has been tried as a mild laxative under the names *Purgatin* and *Purgatol*, but it is a kidney-irritant. The acetyl derivatives of the tetra-alkyl ethers of rufigallic acid have been recommended as purgatives.[3] *Exodin* is said to be the tetramethyl ether of the diacetyl compound, but according to Zernik[4] it is a mixture of several substances, of which the hexamethyl ether is the one to which the purgative action is due, the diacetyl tetramethyl ether being inert. Exodin is a mild purgative.

Many derivatives of aloïn have been prepared which are intended to be free from the bitter taste of the parent substance whilst retaining its purgative action; these, being only slowly decomposed in the intestine, should be more active. A derivative of aloïn and formaldehyde has been prepared in which the methylene group enters into two hydroxyl groups—[5]



$$C_{17}H_{16}O_3(OH)_2 + OCH_2 = C_{17}H_{16}O_5\left<\begin{matrix}O\\O\end{matrix}\right>CH_2 + H_2O.$$

Its action resembles that of aloïn itself. H. Meyer has prepared *tribromaloïn*, $C_{17}H_{15}O_7Br_3$, which has a milder action than aloïn, and triacetyl aloïn, $C_{17}H_{15}O_7(CO.CH_3)_3$, which is as powerful as the parent substance in its action, and has the advantage of being tasteless and keeping well. An oxidation product obtained by the action of persulphate on aloïn[1] has a weak purgative action, and is free from harmful by-effects.

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[1] This statement of course only applies to substances such as these, which act locally. It does not apply to apomorphine, etc.

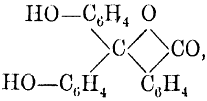
[2] Dixon, "Manual of Pharmacology."

[3] D. R. P., 151,724.

[4] Zernik, *Apoth. Zeit.*, **19**, 598.

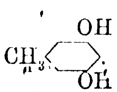
[5] D. R. P., 86,449.

A glucoside having a purgative action has been obtained from *cascara sagrada*, and named *Peristaltin.*

Phenolphthalein,  although not an anthraquinone derivative, has a purgative action without harmful effects on the kidneys, and has attained wide use as a laxative under the names *Purgen* and *Laxin.* It sometimes causes griping, and to overcome this drawback its acetyl-valeryl derivative has been introduced, under the name of *Aperitol.*

Drastic Purgatives.—Very little is known of the chemical nature of these substances, which act by reason of their generally irritant properties. In large doses they give rise to bad effects, but in their specific doses they act more promptly than the anthraquinone derivatives, though they are apt to cause nausea and vomiting.

Croton oil contains a large number of substances, but its intense purgative action is probably due to a resin, $C_{13}H_{18}O_4$.[2] The action of jalap has also been attributed to a resin, which is, however, a mixture of several substances.[3]

The active principle of *podophyllin* is *podophylltoxin*, $C_{15}H_{14}O_6$, a neutral substance, which when heated with alkali forms podophyllinic acid, $C_{15}H_{16}O_7$. By loss of water this acid forms picropodophyllin, $C_{15}H_{14}O_6$, an isomeride of podophyllin, and on further treatment with alkali yields acetic acid and orcine, . *Picropodophyllin* is probably the lactone of *podophyllinic acid*, these substances being regarded as derivatives of γ-pyrone.[4]

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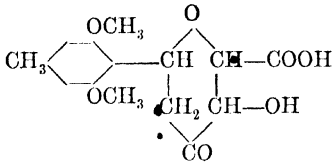
[1] D. R. P., 134,987.

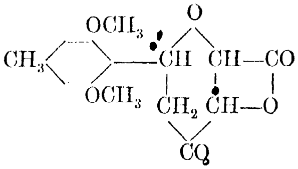
[2] Dunstan and Boole, *Proc. Roy. Soc.*, 58 (1895), 238.

[3] Power and Rogerson, *Pharmaceutical Journal*, 29 (1909), 7; *Journ. of American Chem. Soc.*, 32 (1910), 80.

[4] Dunstan and Henry, *J. C. S.*, 73 (1898), 209.



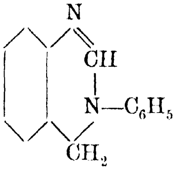
Podophyllinic acid.



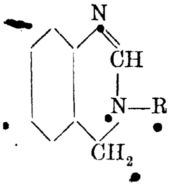
Picropodophyllin.

These two substances are without definite purgative action.[1]

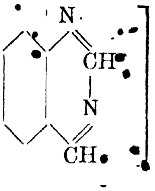
Other Substances acting on the Gastro-Intestinal Tract.—*Phenyl-dihydroquinazoline* was accidentally found to possess a bitter taste, and to produce an early feeling of hunger,



and hence it has been introduced as an aperitive,[2] under the name of *Orexin*. Other substances of this type have also been investigated, but none of them are so satisfactory as this one. Dihydroquinazolines of the type—



Quinazoline is



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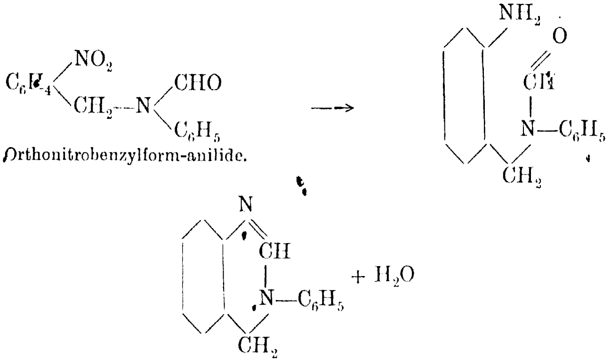
[1] Mackenzie and Dixon, *Edinburgh Med. Journ.* (1898), 134.

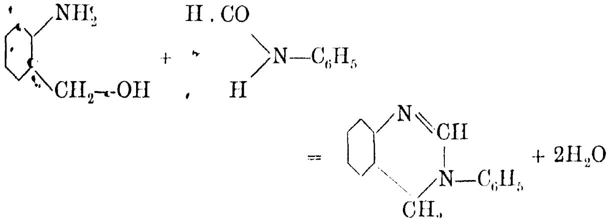
[2] Aperitive denotes a substance used to stimulate the appetite.

are formed by the reduction of orthonitrobenzylform-anilides, -toluides, etc.—[1]



Orthonitrobenzylform-anilide.

Orexin is also prepared by the action of formanilide on ortho-aminobenzyl alcohol—[2]



Orexin is used in the form of the hydrochloride, owing to the bad taste of the free base. The *tannate* is insoluble in water (*cf.* quinine), and therefore is quite tasteless. It is soluble in hydrochloric acid, and therefore dissolves in the gastric contents, and can exert the required action. It is now largely used instead of the hydrochloride.

Coto-bark has a specific effect on the walls of the intestine, dilating them and helping resorption, which renders it of use in diarrhœa. Its active constituent is cotoïn, $C_{14}H_{12}O_4$, a derivative of benzophenone and phloroglucinol having the formula—

$$CH_3O . C_6H_2(OH)_2—CO—C_6H_5.$$

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[1] D. R. P., 51,712.

[2] *Ibid.*, 113,163.

This substance has a sharp taste, and in order to overcome this disadvantage, various derivatives have been prepared, one of which, known as *Fortoïn*, is a methylene-dicotoïn, $CH_2(C_{14}H_{11}O_4)_2$, formed by the action of formaldehyde on cotoïn.[1] It is free from the sharp taste of cotoïn, and is said to have a stronger action, having especially an enhanced bactericidal effect.

Condensation products of cotoïn with phenols have been prepared,[2] which have the antiseptic action of the phenols combined with the beneficial effects of cotoïn on the intestines.

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[1] D. R. P., 104,362.

[2] *Ibid.*, 104,903.

CHAPTER XVII.

VARIOUS OTHER COMPOUNDS OF INTEREST.

Glucosides.—Several glucosides which owe their physiological activity to their hydrolytic cleavage products have been mentioned in other parts of this volume. It will suffice to recall such compounds as salicin and chrysophan. Besides these, there are numerous glucosides which have a powerful and characteristic physiological action of their own. The most important of these are the active principles of digitalis and strophanthus, drugs having a powerful action in increasing the strength and diminishing the frequency of the heart-beat. *Digitalis* contains several active glucosides, but unfortunately very little is known of their chemical constitution beyond the fact that most of them are derivatives of substances allied to cholesterin. The most important are *digitalin* and *digitoxin;* the latter, on warming with caustic soda, yields the physiologically inert digitoxic acid. The active constituent of *strophanthus* is a glucoside, *strophanthin*, $C_{40}H_{66}O_{19}$, which on hydrolysis yields strophanthidin, $C_{27}H_{38}O_7$, and a carbohydrate, $C_{13}H_{24}O_{10}$. Strophanthidin contains two lactone groupings, a benzene nucleus, an unsaturated linkage, —CH=CH—, and probably three hydroxyl groups. The carbohydrate, $C_{13}H_{24}O_{10}$, is the methyl ether of a biose, $C_{12}H_{22}O_{10}$.[1]

Various other important glucosides have been mentioned in the previous chapter.

Many physiologically active compounds are "glucosides" derived from pentoses instead of hexoses. Frangulin (*cf.* p. 226), is an example of a pentose derivative, and more recently it has been shown that the poisonous hæmolytic substance present in the fungus *Amanita phalloides* is a pentoside.

Within recent years a considerable number of glucosides have been obtained synthetically, some of these being identical with natural products. For example, E. Fischer[1] has obtained *dl.* mandelonitrile glucoside, identical with *prulaurasin*; this has been resolved into its dextro and lævo components, and the former found to be identical with *sambunigrin*, a glucoside occurring in the leaves of the elder.

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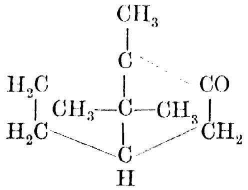
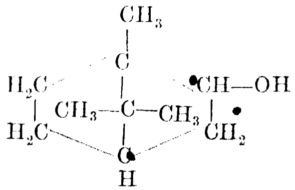
[1] Feist, *Ber.*, **33** (1900), 2061, 2069, 2091; Fraser, "Strophanthus," Edinburgh (1887); Arnaud, *C. R.*, **107** (1888), 181, 1012.

Unfortunately, however, the glucosides of greatest importance medicinally have not yet been synthesized, and are mostly of unknown structure. For this reason, and owing to the fact that very few synthetic derivatives have been prepared from them, the glucosides, in spite of their great physiological and practical importance, lie rather beyond the scope of this book.

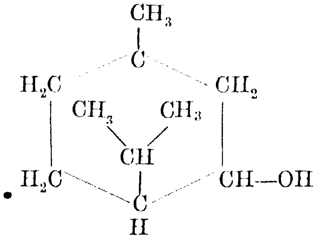
Camphor and the Terpenes.—The substances of the camphor group show a general resemblance to one another in their physiological action.



Camphor.



Borneol.



Menthol.

All three have an antiseptic and slight local anæsthetic action. *Borneol*, known also as Borneo camphor, has less local irritant action, and can be tolerated in larger doses than camphor. *Menthol* is not much used internally, but it finds employment as a mild local anæsthetic. *Camphor* is the most important of these substances, and, as is well known, is obtained from the camphor-laurel, growing in China, Japan, and the East Indies, but within recent years it has also been produced artificially from turpentine.

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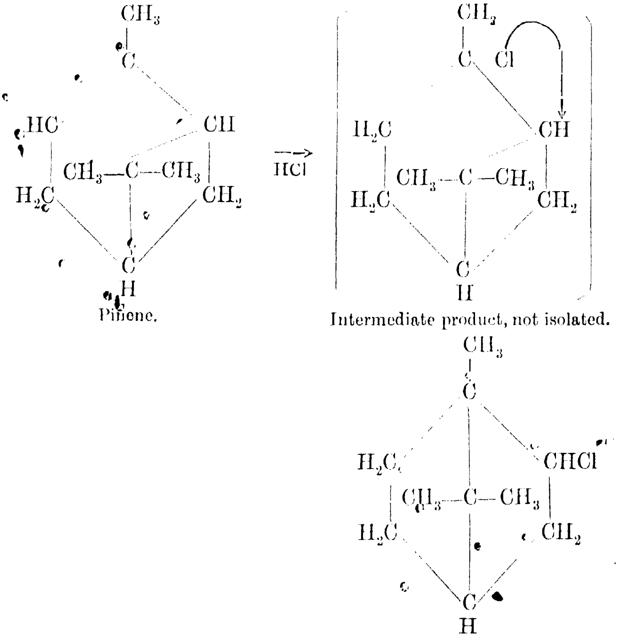
[1] Fischer and Bergmann, *Ber.*, 50 (1917), 1047.

It is a carminative and is used to check colds in the head, and for a very large variety of other medicinal purposes. It is injected as a stimulant in cases of collapse.

It is necessary to distinguish between the so-called "artificial" or "synthetic camphor," and true camphor produced artificially. The former is in reality not camphor at all, but is "pinene hydrochloride," obtained by the action of dry hydrogen chloride on turpentine. Turpentine consists chiefly of pinene, and on treatment with dry hydrochloric acid, the crystalline "pinene hydrochloride" is formed. This substance, which resembles camphor in many of its properties, is bornyl chloride, an intramolecular change taking place when hydrogen chloride acts on pinene.

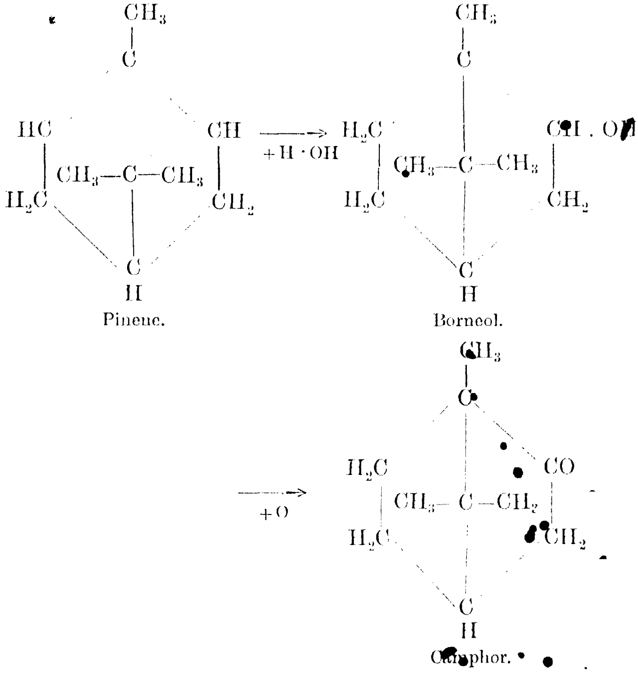


Pinene.

Intermediate product, not isolated.

ornyl chloride (" Pinene chloride ").

True camphor has been completely synthesized, but the synthesis is an extremely lengthy and laborious one, and is impracticable as a commercial process. Camphor can, however, be economically prepared from turpentine (pinene) by a simple series of reactions. Turpentine on heating with anhydrous oxalic acid at 120°-130° C., yields camphor, borneol, and the oxalic and formic esters of borneol.[1]



The borneol esters are hydrolyzed, and the resultant borneol oxidized to camphor by means of dichromate and sulphuric acid.[2]

Various other methods of oxidizing borneol to camphor have been devised, using permanganate,[3] nitric acid,[4] chromic acid,[5] air,[6] or ozone[7] as the oxidizing agent.

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[1] D. R. P., 134,553.

[2] *Ibid*., 220,838; E. P., 21,946 (1907).

[3] D. R. P., 157,590.

[4] *Ibid*., 217,555.

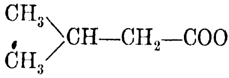
[5] *Ibid*., 158,717.

[6] *Ibid*., 161,523, 166,722.

[7] *Ibid*., 161,306.

Valerianic Acid Derivatives.—These are used as nervous sedatives, and some of them, containing bromine and iodine, have already been mentioned in Chapter XIII.

The esters of borneol and menthol with isovalerianic acid,

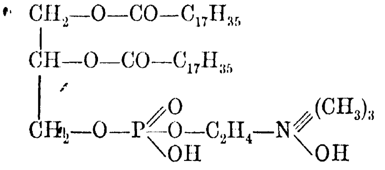


$$\begin{matrix} CH_3 \\ CH_3 \end{matrix} \rangle CH-CH_2-COOH$$

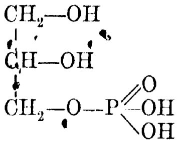
are known as *Bornyval* and *Validol* respectively. *Gynoval* is the *iso*-borneol ester of the same acid, and *Valyl* is the diethyl-amide $(CH_3)_2 . CH . CH_2 . CO . N(C_2H_5)_2$. It will be seen that this also contains the grouping $—CO.N(C_2H_5)_2$ which is present in many other hypnotic and sedative compounds. *New Bornyval* is bornyl isovalerylglycollate,

$(CH_3)_2 . CH . CH_2 . CO . O—CH_2—CO . O . C_{10}H_{17}$.

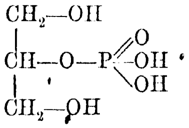
Glycerophosphates.—One of the chief constituents of nervous tissue is lecithin, a complex ester of choline and distearylglycerophosphoric acid, the composition of which is indicated by some such formula as—



In reality it is somewhat more complex, for it contains also the corresponding derivatives of various other fatty acids such as palmitic, $C_{16}H_{32}O_2$, and of unsaturated acids such as oleic, $C_{18}H_{34}O_2$, and linoleic, $C_{18}H_{32}O_2$, as well as that from stearic acid, $C_{18}H_{36}O_2$. On hydrolysis it yields a glycerophosphoric acid which is probably a mixture[1] of the α and β acids—



α-acid.



β-acid.

As lecithin is said[2] to exert a favourable influence on growth and metabolism, glycerophosphoric acid and its salts have been introduced into therapeutics. It is, however, improbable that lecithin is built up in the body from glycerophosphoric acid, and it is doubtful whether glycerophosphates have any advantage over the inorganic hypophosphites.

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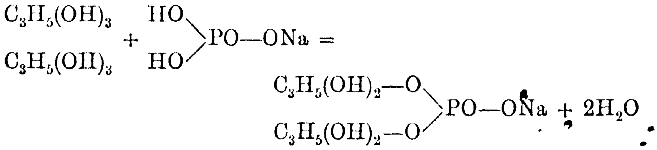
[1] O. Bailly, *C. R.*, 160 (1915), 395.

[2] Danilewski, *C. R.*, 121 (1895), 1167; 123 (1896), 195.

Glycerophosphoric acid is prepared by the action of phosphorus pentoxide on glycerol,[1] or by heating phosphoric acid with glycerol for six days.[2]

A better result is obtained if the glycerol and syrupy phosphoric acid are heated for twenty-four to twenty-eight hours at 100°-105° in a vacuum.[3]

Sodium glycerophosphate may be obtained[4] by heating two molecules of glycerol with one molecule of monosodium or monoammonium phosphate in a vacuum, whereby a diglycerylmonometallic phosphate is formed.



$$\begin{matrix} C_3H_5(OH)_3 \\ C_3H_5(OH)_3 \end{matrix} + \begin{matrix} HO \\ HO \end{matrix}\!\!>PO{-}ONa = \begin{matrix} C_3H_5(OH)_2{-}O \\ C_3H_5(OH)_2{-}O \end{matrix}\!\!>PO{-}ONa + 2H_2O$$

This is then saponified by caustic soda solution, and disodium glycerophosphate separates out on concentration.

The crystalline sodium salt thus obtained has been shown to be identical with that of the β-glycerophosphoric acid obtained synthetically,[5] and this conclusion as to its constitution has been confirmed by an indirect method.[6]

The sodium salt is very soluble in water, the calcium salt moderately soluble in cold water, but almost insoluble in hot. The ferric salt is soluble, and therefore can be used to combine the tonic properties of iron and phosphorus.

In the preparation of the crystalline sodium salt, there is always some uncrystallizable mother liquor, rich in glycerophosphate. This probably contains some of the sodium salt of the α-acid. The salts of this acid have been obtained synthetically by the action of trisodium phosphate on α-monochlorhydrin, $CH_2Cl . CH(OH) . CH_2 . OH$,[1] and by the oxidation of sodium monoallylphosphate.[2]

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[1] Pelouze, *Journ. prakt. Chem.*, **36** (1845), 257.

[2] Portes, Prunier, *Bul.*, [3] **13** (1895), 96.

[3] E. P., 280[illegible] (1912). See also E. P., 2881 (1912), and E. P., 19,319 (1911).

[4] French Patent, 373,112.

[5] King and Pyman, *J. C. S.*, **105** (1914), 1238.

[6] Grimbert and Bailly, *C. R.*, **160** (1915), 207.

$$CH_2 : CH—CH_2—O—PO(ONa)_2 \rightarrow$$
$$CH_2(OH)—CH(OH)—CH_2—O—PO(ONa)_2.$$

Bromo-lecithin is said to differ from lecithin in being absorbed in the intestine as such, without being split up into glycerophosphoric acid. It is prepared by saturating a chloroform solution of lecithin with bromine and drying *in vacuo*.[3] Jodo-lecithin has also been prepared.[4]

Sulphur Compounds.—In this section are included various compounds containing sulphur. For the most part, they are not related to one another, but are brought together here for convenience.

Ichthyol is one of the best known of these. It is a substance of unknown composition, containing sulphur, obtained by the destructive distillation of "stink-stone" or "oil-stone," a deposit of fossil fish found in the Tyrol and southern Bavaria. By the action of sulphuric acid on the volatile basic oil thus produced, a sulphonic acid is formed, the salts of which are used medicinally. The ammonium salt of this ichthyol-sulphonic acid is a reddish-brown syrup, soluble in water, and is often known simply as "*Ichthyol.*" It is used both externally and internally for skin diseases, and is also used internally in tuberculosis and many other complaints, and as an intestinal antiseptic. The lithium and sodium salts are also used, and the zinc salt is used externally.

The disagreeable smell and taste of ichthyol are said to be largely due to impurities, and it can be obtained in a purer form by steam distillation in a vacuum.[5]

Ichthalbin is an odourless and tasteless powder, obtained by precipitating an albumen solution with a solution of ichthyol-sulphonic acid.[6] It is used in the treatment of eczema and of intestinal catarrh. A compound of ichthyol-sulphonic acid and formaldehyde,[7] is known as *Ichthoform*. It is a dark coloured powder insoluble in water, and with very little taste or odour.

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[1] King and Pyman, *loc. cit.*

[2] O. Bailly, *C. R.*, 160 (1915), 163.

[3] D. R. P., 156,110.

[4] *Ibid.*, 155,629.

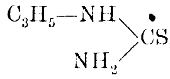
[5] *Ibid.*, 118,452.

[6] *Ibid.*, 100,707, 124,144.

[7] *Ibid.*, 107,233.

t is used internally as an intestinal antiseptic, and externally as a dressing for wounds (iodoform substitute).

Triphenylstibine sulphide, $(C_6H_5)_3$ SbS, is used under the name of *Sulphoform* in skin diseases as it liberates nascent sulphur on the skin.

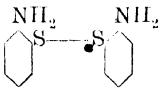


Allyl-thiourea, $\begin{matrix}C_3H_5-NH\\NH_2\end{matrix}\Big\rangle CS$, known as *Thiosinamine*, a substance of some importance as a drug. It is formed by the action of ammonia on allyl-mustard oil,

$$C_3H_5 - N:C:S + NH_3 = C_3H_5.NH.CS.NH_2,$$

and is a white crystalline substance moderately soluble in water. It is administered by hypodermic injection for the treatment of upus, and for softening scar-tissues. Its sparing solubility in water is a drawback, and more concentrated solutions can be obtained by dissolving it with half a molecular proportion of sodium salicylate.[1] This solution is known as *Fibrolysin*, and t is claimed that the presence of the sodium salicylate not only ncreases the solubility, but also renders the injection less painful. It has been extensively used in relaxing scar-tissue. The additive compound of thiosinamine with ethyl iodide, $C_3H_5.NH.CS.NH_2, C_2H_5I$, is known as *Tiodine*, and is readily soluble in water giving solutions said to be painless on njection. *Iodolysin* is a similar soluble, non-irritant preparation of thiosinamine. It is said to contain 43 per cent. of thiosinamine, and 47 per cent. of iodine.

Recently successful results have been claimed for a sulphur compound in the treatment of syphilis.[2] This is di-*o*-aminophenyl disulphide,



known as *Intramine*. It is obtained by the oxidation of orthoaminophenyl mercaptan with ferric chloride, and is a pale yellow crystalline compound insoluble in water. It is administered by intramuscular injection of a suspension in olive oil.

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[1] D. R. P., 163,804.

[2] McDonagh, *Lancet*, 190 (1916), 238.